56

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(54) Title: SOLID ORAL DOSAGE FORM CONTAINING HEPARIN OR A HEPARINOID IN COMBINATION WITH A CARRIER

(57) Abstract

A solid oral dosage form containing a heparin drug in admixture with a carrier such that the dosage form protects the carrier from precipitation during transit through the low pH regions of the GI track, thus enabling concurrent presentation of the heparin drug and the carrier in the GI track to facilitate the absorbtion and/or enhance the bioavailability of the heparin drug. The carrier is selected fron the group consisting of SNAC, SNAD, pharmaceutically acceptable salts thereof, esters thereof and combinations thereof.

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SOLID ORAL DOSAGE FORM CONTAINING HEPARIN OR AN HEPARINOID IN COMBINATION WITH A CARRIER

25   for which the following is a specification.

SOLID ORAL DOSAGE FORM CONTAINING HEPARIN OR AN
HEPARINOID IN COMBINATION WITH A CARRIER

FIELD OF THE INVENTION

The present invention relates to a solid oral dosage form containing a carrier in combination with a Heparin or a heparinoid. In particular, the invention relates to a solid oral dosage form comprising a Heparin or a heparinoid as an active ingredient in combination with a carrier such that the carrier enhances the bioavailability and/or the absorption of the active ingredient.

BACKGROUND OF THE INVENTION

The epithelial cells lining the lumenal side of the GIT are a major barrier to drug delivery following oral administration. However, there are four recognised transport pathways which can be exploited to facilitate drug delivery and transport: the transcellular, paracellular, carrier-mediated and transcytotic transport pathways. The ability of a drug, such as a conventional drug, a peptide, a protein, a macromolecule or a nano- or microparticulate system, to "interact" with one or more of these transport pathways may result in increased delivery of that drug from the GIT to the underlying circulation.

Certain drugs utilise transport systems for nutrients which are located in the apical cell membranes (carrier mediated route). Macromolecules may also be transported across the cells in endocytosed vesicles (transcytosis route). However, many drugs are transported across the intestinal epithelium by passive diffusion either through cells (transcellular route) or between cells (paracellular). Most orally administered drugs are absorbed by passive transport. Drugs which are lipophilic permeate the epithelium by the transcellular route whereas drugs that are hydrophilic are restricted to the paracellular route.

-3-

Paracellular pathways occupy less than 0.1% of the total surface area of the intestinal epithelium. Further, tight junctions, which form a continuous belt around the apical part of the cells, restrict permeation between the cells by creating a seal between adjacent cells. Thus, oral absorption of hydrophilic drugs such as peptides can be

5   severely restricted. Other barriers to absorption of drugs may include hydrolysing enzymes in the lumen brush border or in the intestinal epithelial cells, the existence of the aqueous boundary layer on the surface of the epithelial membrane which may provide an additional diffusion barrier, the mucus layer associated with the aqueous boundary layer and the acid microclimate which creates a proton gradient across the

10   apical membrane. Absorption, and ultimately bioavailability, of a drug may also be reduced by other processes such as P-glycoprotein regulated transport of the drug back into the gut lumen and cytochrome P450 metabolism.

Therefore, new strategies for enhancing the delivery of drugs such as Heparin and/or heparinoids across the GIT cell layers are needed. Often, however, the

15   enhancement of drug absorption correlates with damage to the intestinal wall. Consequently, limitations to the widespread use of GIT enhancers is frequently determined by their potential toxicities and side effects. Additionally and especially with respect to peptide, protein or macromolecular drugs, the "interaction" of the GIT enhancer with one of the transport pathways should be transient or reversible, such as

20   a transient interaction with or opening of tight junctions so as to enhance transport via the paracellular route.

US 5,650,386 and WO96/30036 (Emisphere Technologies, Inc.) disclose modified amino acid compounds useful for the effective administration, including oral administration, of a variety of active agents including heparin. US 5,650,386 and

25   WO96/30036 are hereby incorporated in their entirety. The modified amino acid compounds disclosed include the two carriers which are referred herein as SNAC and SNAD and whose chemical identities are given below:

-4-

SNAC   8-(salicyloylamino)octanoic acid

SNAD   10-(salicyloylamino)decanoic acid
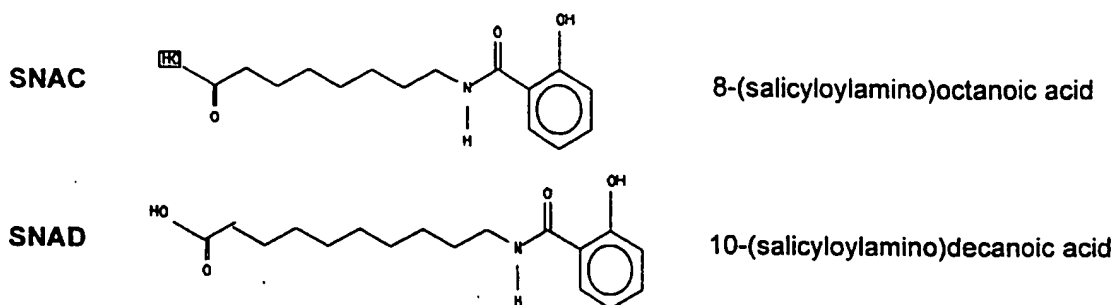
SNAC and SNAD have been shown to promote the oral absorption of heparin in a number of animal models, e.g., rats and primates, and SNAC has been shown to promote the oral absorption of heparin in man, giving measurable changes in APTT and

5   anti-FXa activity. The combination carrier/heparin in these studies have been administered in an aqueous solution containing, e.g., 25% propylene glycol as a cosolvent and possibly as an enhancer. The carriers SNAC and SNAD have a very bitter taste and tolerability issues were observed when the aqueous solutions were administered to man. A taste-masked solution has been developed in order to improve

10   tolerability and was subsequently dosed in a human biostudy, at a dose of 2.25g SNAC in 30 mls of taste-masked solution, with increasing doses of heparin from 30,000 to 150,000 iu. No adverse events were reported in the study. The pharmacokinetic profiles observed show a very rapid increase in APTT and anti-FXa activity which declines very rapidly (elimination T½ calculated from the biostudy in man was 1.45 -

15   1.63 hours compared to 2.45 hours for the dose administered s.c.). Daily dosing of every 5 hours will therefore be required for the oral solution which may give rise to possible tolerability issues and patient compliance problems.

Provision of a solid oral dosage form which would facilitate the administration of a drug together with the carrier is desirable. The advantages of solid oral dosage forms

20   over other dosage forms include ease of manufacture, the ability to formulate different controlled release and extended release formulations and ease of administration. Administration of drugs in solution form does not readily facilitate control of the profile of drug concentration in the bloodstream. Solid oral dosage forms, on the other hand, are versatile and may be modified, for example, to maximise the extent and duration of drug

25   release and to release a drug according to a therapeutically desirable release profile.

-5-

There may also be advantages relating to convenience of administration increasing patient compliance and to cost of manufacture associated with solid oral dosage forms.

SUMMARY OF THE INVENTION

Surprisingly, it has been found that the combination of a carrier with a heparin drug is more effective when a solid oral dosage form is designed to present the drug and carrier concurrently to the GI tract, the drug and carrier preferably being in solubilized forms, in a manner that allows the carrier to facilitate the absorption of therapeutically effective amounts of the drug in an animal, preferably a human. Thus, solid oral dosage forms comprising a heparin drug in combination with a carrier are provided according to the present invention. Preferably, the solid oral dosage form targets both the carrier and the heparin drug for release in the lower GI tract. More preferably, the solid oral dosage form substantially prevents precipitation of the carrier in the regions of the GI track in which the pH is low. The solid oral dosage forms according to the invention have a number of advantages, including 1) protection for the carrier from precipitation at low pH, 2) release of both carrier and drug at a pH of approximately 6.5 or greater to allow for solulibilzation of the carrier; 3) flexibility in extent and duration of both the drug and carrier release; 4) ability to decrease the dosing frequency; 5) ability to effectively taste mask and 6) production of a more stable product compared to a liquid product.

The present invention provides a solid oral dosage form containing a heparin drug in admixture with a carrier such that the dosage form protects the carrier from precipitation during transit through the low pH regions of the GI track, thus enabling concurrent presentation of the heparin drug and the carrier in the GI track to facilitate the absorbtion and/or enhance the bioavailability of the heparin drug. The carrier is selected from the group consisting of SNAC, SNAD, pharmaceutically acceptable salts thereof, esters thereof and combinations thereof.

-6-

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the dissolution profile of SNAC from SNAC/Heparin IR (tablets D) and SR tablets G (SR component added extragranularly) and SR tablets H (SR component added intragranularly at pH 1.2 and pH 7.4 according to Example 3;

5   Figure 2 shows the dissolution profile of Heparin from SNAC/Heparin IR (tablets D) and SR tablets G (SR component added extragranularly) and SR tablets H (SR component added intragranularly at pH 1.2 and pH 7.4 according to Example 3;

Figure 3 shows a plot of Anti-Xa Activity (IU/ml) versus time following oral administration of the following formulations to dogs as described in Example 4: a)
10   three uncoated solid oral dosage tablets each containing 450 mg Heparin USP and 1.1g SNAC as given in Example 2; b) three coated (Eudragit S) solid oral dosage tablets each containing 450 mg Heparin USP and 1.1g SNAC as given in Example 2; 3) 7.5 ml of a 20% PG aqueous solution containing 450 mg Heparin and 1.1 SNAC; and 4) 7.5 ml of an aqueous solution containing 450 mg Heparin and 1.1 SNAC;

15   Figure 4 shows the dissolution profiles of SNAD and Heparin USP at pH 1.2 and pH 7.4 from SNAD/Heparin IR tablets (Tablet P formulation as shown in Example 5); and

Figure 5 shows the mean antifactor Xa levels versus time following administration of the following treatments to dogs as described in Example 7: 1)
20   Uncoated USP heparin tablet (90,000 IU + 550 mg SNAD); two tablets/dog; 2) LMW Heparin solution (90,000 IU + 550 mg SNAD in water); 10 ml/dog; 3) Uncoated LMW heparin tablet (90,000 IU + 550 mg SNAD); two tablets/dog; 4) LMW heparin subcutaneous (5000 IU in 0.5 ml saline); 5) LMW Heparin solution (90,000 IU + 1100 mg SNAD in water); 10 ml/dog; and 6) Uncoated LMW heparin tablets (90,000 IU +
25   1100 mg SNAD); 3 tablets/dog.

DETAILED DESCRIPTION OF THE INVENTION

As used in this specification and appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus,

-7-

for example, reference to "a carrier" includes a mixture of one or more carriers, reference to "a drug" includes reference to one or more drugs, and the like.

As used herein, the term "carrier" refers to SNAC or SNAD, pharmaceutically acceptable salts thereof, esters thereof and combinations thereof. Preferably, the
5   carrier is SNAC or SNAD or a sodium salt thereof.

As used herein, the term "drug" or "heparin drug" includes heparins, such as Heparin USP, low molecular weight heparins (LMWH), unfractionated heparins, heparin fragments and heparinoids, pharmaceutically acceptable salts thereof and combinations thereof. The term "drug" or "heparin drug" also includes nano- or microparticulate drug
10   delivery systems in which a drug is entrapped, encapsulated by, associated with, or attached to a nano- or microparticle. The drug itself may be in the form of nano-, micro- or larger particles in crystalline or amorphous form.

As used herein, a "therapeutically effective amount of a drug" refers to an amount of drug that elicits a therapeutically useful response in an animal.

15   As used herein, a "therapeutically effective amount of a carrier" refers to an amount of carrier that allows for uptake of therapeutically effective amounts of the drug via oral administration

A solid oral dosage form according to the present invention may be a tablet or may be a multiparticulate. The term "tablet" as used herein includes, but is not limited
20   to, immediate release (IR) tablets, sustained release (SR) tablets, matrix tablets, multilayer tablets, multilayer matrix tablets extended release tablets, delayed release tablets and pulsed release tablets any or all of which may optionally be coated with one or more coating materials, including polymer coating materials, such as enteric coatings, rate-controlling coatings, semi-permeable coatings and the like. The term
25   "tablet" also includes osmotic delivery systems in which a drug compound is combined with an osmagent (and optionally other excipients) and coated with a semi-permeable membrane, the semi-permeable membrane defining an orifice through which the drug compound may be released. Tablet solid oral dosage forms particularly useful in the practice of the invention include those selected from the group consisting of IR tablets,

-8-

SR tablets, coated IR tablets, matrix tablets, coated matrix tablets, multilayer tablets, coated multilayer tablets, multilayer matrix tablets and coated multilayer matrix tablets.

The term "multiparticulate" as used herein means a plurality of discrete particles, pellets, mini-tablets and mixtures or combinations thereof. If desired, the

5   multiparticulate may be coated with a layer containing rate controlling polymer material. Alternatively, the multiparticulate and one or more auxiliary excipient materials can be compressed into tablet form. Such a tablet may optionally be coated with a controlled release polymer so as to provide additional controlled release properties.

A number of preferred embodiments of the invention will now be described. In

10   each case the drug may be present in any amount which is sufficient to elicit a therapeutic effect and, where applicable, may be present either substantially in the form of one optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers. The drug compound is suitably present in any amount sufficient to elicit a therapeutic effect. As will be appreciated by those skilled in the art, the actual amount of drug

15   compound used will depend on the potency of the drug compound in question. The carrier is suitably present in any amount sufficient to allow for uptake of therapeutically effective amounts of the drug via oral administration. Preferably the drug and the carrier are present in a ratio of from 100: 1 to 1:100 (drug : carrier), preferably 10:1 to 1:10. The actual ratio of drug to carrier used will depend on the potency of the drug

20   compound and the enhancing activity of the carrier.

In a first embodiment, a solid oral dosage form according to the invention comprises a drug and a carrier in admixture compressed into a tablet.

In a second embodiment, a solid oral dosage form according to the invention comprises a drug, a carrier and a rate controlling polymer material in admixture

25   compressed into a tablet. The term "rate controlling polymer material" as used herein includes hydrophilic polymers, hydrophobic polymers and mixtures of hydrophilic and/or hydrophobic polymers that are capable of controlling or retarding the release of the drug compound from a solid oral dosage form of the present invention. Suitable rate controlling polymer materials include those selected from the group consisting of

30   hydroxyalkyl cellulose such as hydroxypropyl cellulose and hydroxypropyl methyl

-9-

cellulose; poly(ethylene) oxide; alkyl cellulose such as ethyl cellulose and methyl cellulose; carboxymethyl cellulose, hydrophilic cellulose derivatives; polyethylene glycol; polyvinylpyrrolidone; cellulose acetate; cellulose acetate butyrate; cellulose acetate phthalate; cellulose acetate trimellitate; polyvinyl acetate phthalate;

5   hydroxypropylmethyl cellulose phthalate; hydroxypropylmethyl cellulose acetate succinate; polyvinyl acetaldiethylamino acetate; poly(alkylmethacrylate) and poly (vinyl acetate). Other suitable hydrophobic polymers include polymers and/or copolymers derived from acrylic or methacrylic acid and their respective esters, zein, waxes, shellac and hydrogenated vegetable oils. Particularly useful in the practice of the present

10   invention are poly acrylic acid, poly acrylate, poly methacrylic acid and poly methacrylate polymers such as those sold under the Eudragit tradename (Rohm GmbH, Darmstadt, Germany) specifically Eudragit® L, Eudragit® S, Eudragit® RL, Eudragit® RS coating materials and mixtures thereof.

     In a third embodiment, a solid oral dosage form according to the invention

15   comprises a multilayer table. Typically such a multilayer tablet may comprise a first layer containing a drug and a carrier in an instant release form and a second layer containing a drug and a carrier in a sustained, extended, controlled or modified release form. In an alternative embodiment, a multilayer tablet may comprise a first layer containing a drug and a second layer containing a carrier. Each layer may

20   independently comprise further excipients chosen to modify the release of the drug or the carrier. Thus the drug and the carrier may be released from the respective first and second layers at rates which are the same or different. Alternatively, each layer of the multilayer tablet may comprise both drug and carrier in the same or different amounts.

     A fourth embodiment a solid oral dosage form according to the invention

25   comprises a drug and a carrier in admixture in the form of a multiparticulate. The drug and carrier may be contained in the same or different populations of particles, pellets or mini-tablets making up the multiparticulate. If the solid oral dosage form is a multiparticulate, capsules such as hard or soft gelatin capsules can suitably be used to contain the multiparticulate. A multiparticulate solid oral dosage form according to the

30   invention may comprise a blend of two or more populations of particles, pellets or mini-tablets having different *in vitro* and/or *in vivo* release characteristics. For example, a

-10-

multiparticulate oral dosage form may comprise a blend of an immediate release component and a delayed release component contained in a suitable capsule.

In the case of any of the abovementioned embodiments, a controlled release coating may be applied to the final dosage form (tablet, multilayer tablet etc.). The
5   controlled release coating may typically comprise a rate controlling polymer material as defined above. The dissolution characteristics of such a coating material may be pH dependent or independent of pH.

The various embodiments of the solid oral dosage forms of the invention may further comprise auxiliary excipients such as for example diluents, lubricants,
10 disintegrants, plasticisers, anti-tack agents, opacifying agents, pigments, flavourings and such like. As will be appreciated by those skilled in the art, the exact choice of excipients and their relative amounts will depend to some extent on the final dosage form.

Suitable diluents include for example pharmaceutically acceptable inert fillers
15 such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose such as that sold under the Trademark Avicel (FMC Corp., Philedelphia, PA) for example Avicel™ pH101, Avicel™ pH102 and Avicel™ pH112; lactose such as lactose monohydrate, lactose anhydrous and Pharmatose DCL21; dibasic calcium
20 phosphate such as Emcompress; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal silicon dioxide such as Aerosil™ 200; talc; stearic acid, magnesium stearate, and calcium stearate.

Suitable disintegrants include for example lightly crosslinked polyvinyl
25 pyrrolidone, corn starch, potato starch, maize starch and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate and combinations and mixtures thereof.

-11-

Example 1:   SNAC and Heparin USP in-vitro precipitation experiments

Mechanisms for SNAC/SNAD enhancement of Heparin absorption in the GI tract have been suggested. These mechanisms include microparticle formation upon exposure to acidic conditions and structure activity relationships between SNAC/SNAD
5   and Heparin or heparinoids. It has been speculated that SNAC and/or SNAD may form a co-precipitate with Heparin or a heparinoid on transit through the GI tract and this co-precipitated complex may play a role in the increased Heparin/heparinoid absorption. The experiments described in this Example elucidate the behavior of the carrier SNAC in combination with Heparin upon contact with the changing environments found in
10   transit through the GI tract and predict that a dosage form containing Heparin/SNAC should target delivery of the Heparin/SNAC combination at the lower GI tract (pH 6.8 - 7.4).

SNAC is the sodium salt of a weak acid with a pKa of 5.01. At low pH, the solubility of SNAC decreases and the SNAC precipitates as the SNAC free acid form.
15   Heparin is also the sodium salt of an acid, heparinic acid, and in acid conditions the Heparin sodium may be converted to the less soluble heparinic acid which may also precipitate out of solution. The activity of Heparin in acid conditions may decrease also as a result of desulphonation.

A number of human biostudies have been carried out to investigate the influence
20   of Heparin and SNAC dose and concentration on the absorption of Heparin from the gastrointestinal tract. It was seen from these studies that Heparin absorption was not only influenced by the dose of Heparin and SNAC administered but also the concentration of SNAC.

In an attempt to explain the influence of SNAC dose and concentration on
25   Heparin absorption a number of precipitation experiments were carried out. The objective of these precipitation studies was to determine the physical behaviour of SNAC and Heparin during transit through the GI tract after oral administration specifically to determine the effect of the different pH environments of the gastrointestinal regions on the level of SNAC and Heparin in solution. Therefore, the in
30   vitro conditions of these experiments were chosen to simulate the 'in vivo' human conditions experienced during oral administration of SNAC/Heparin solutions. Solutions

-12-

were added to dilution medium of simulated gastric fluid (GIF) (0.1N HCl with 0.2 w/v
NaCl, actual pH 1.24-1.31) or 0.1N HCl (pH 1.2) to assess the effect of the acidic
environment of the stomach on these oral solutions. The resulting suspensions were
further diluted with isotonic phosphate buffers of pH 6.2, 6.8 and 7.4, to mimic the
5   increasing alkaline conditions along the gastrointestinal tract.

The SNAC/Heparin solutions investigated were equivalent to solutions dosed in
the biostudies (75mg/ml SNAC with 1,000IU/ml and 3,000IU/ml Heparin in 30ml of 20%
aq. propylene glycol (PG) and 150mg/ml SNAC with 428IU/ml Heparin in 70ml of 20%
aq. PG). These solutions were chosen to examine both the effect of increasing the
10 Heparin dose and keeping the SNAC dose and concentration constant and to examine
the effect of increasing the dose and concentration of SNAC and keeping the dose of
Heparin constant. Corresponding solutions of SNAC (75mg/ml in 30ml of 20% aq. PG)
and Heparin (333IU/ml, 1,000IU/ml and 3,000IU/ml in 30ml of 20% aq. PG) were also
examined to assess the behaviour of the individual components of these solutions in the
15 various pH environments.

Diluting with simulated GIF, pH 1.2
The required volumes of 30ml or 70ml of Heparin, SNAC and SNAC/Heparin
solutions were added to 100mls of simulated GIF at 37°C and gently stirred. A 10ml
sample of the resulting suspension/solution was removed for further dilution studies.
20 The remaining suspension was filtered using a Millipore pump and 0.45µm filter paper.
The filtered precipitate was dried under vacuum at ambient temperature and the
precipitate weight was recorded. The precipitate was characterised as detailed below.
The Heparin and/or SNAC content of the filtrate or solution formed was assayed. The
percentage of SNAC and Heparin in solution and precipitated was based on their
25 theoretical concentrations in the original Heparin and/or SNAC solutions. The pH of
these solutions was measured before and after dilution.

Diluting with dilution medium pH 6.2, pH 6.8 and pH 7.4
A sample of the suspension formed after dilution with GIF was diluted (1:10) with
isotonic phosphate buffers pH 6.2, pH 6.8 and pH 7.4. The resulting
30 solution/suspension was then recovered and characterised as described above. When
a suspension was observed after dilution, a Millipore pump and 0.45µm filter were used

-13-

to separate the precipitate which was dried under vacuum and the weight of the dried precipitate was recorded.

Characterisation of precipitate

Particle size analysis of suspension was carried out using a Malvern
5   Mastersizer. The suspension to be analysed was dispersed in filtered H_2O in the stirred small volume cell. A 300mm lens was used and a 3OHD presentation. The particle size analysis was repeated in triplicate. DSC analysis was carried out using a Perkin Elmer DSC 7. Approximately 5mg of the sample to be analysed was weighed into an aluminum pan and scanned between 40°C and 230°C at a scanning rate of 10°C/min, in
10   an atmosphere of N_2. XRD analysis was carried out using a Siemens XRD. A powdered sample was placed on a glass slide and the XRD pattern was measured between 5° and 35° two theta at a rate of 0.05°/sec.

SNAC and Heparin assays

SNAC analysis was carried out using a HPLC method. The HPLC conditions
15   were as follows: column-TCD 137 Hypersil BDS C18 5μ (50 x 4.6mm), wavelength-244nm, flow rate-2ml/min, temperature-ambient, injection volume-50μm, run time-20 minutes. Two mobile phases A and B were used for gradient. The mobile phase A was 900mls d.H_2O, 100mls Acetonitrile, 2.5ml 1N HCl, 2ml Acetic acid. The mobile phase B was 300mls d.H_2O, 700mls Acetonitrile, 3mls Acetic acid. The diluting solvent used
20   was a ratio of Mobile phase B to d.H_2O of 3:2.

The Heparin analysis was carried out using an anti-FXa assay kit, Coatest® supplied by Chromogenix. The Heparin is analysed as a complex [Heparin·AT] with excess Antithrombin. The amount of FXa neutralised by the complex [Heparin·AT] is proportional to the amount of complex and hence Heparin. The remaining FXa
25   hydrolyses the chromogenic substrate S-2222 thus liberating the chromophoric group, pNA. The colour is then read photometrically at 405nm and the remaining FXa can be determined thus allowing the amount of Heparin to be calculated.

SNAC solution (75mg/ml)

An aqueous solution of 20% PG containing SNAC without Heparin was initially
30   investigated to determine the effect of the various pH environments on SNAC in

-14-

solution. The dose and concentration of SNAC in solution were 2.25g SNAC and 75mg/ml SNAC, respectively.

When the 30ml solution was added to simulated GIF, a percentage of the SNAC precipitated from solution. When the SNAC solution was added to a 0.1N HCl dilution medium, a higher percentage of SNAC was precipitated as shown in Table 1. Therefore, the SNAC concentration in the supernatant of the SNAC solutions diluted with GIF was greater (3.80mg/ml) than the concentration in the supernatant diluted with 0.1N HCl (0.015mg/ml). Dissolved salicyclic acid was detected in the samples of SNAC solutions diluted with 0.1N HCl.

Table 1: The influence of dilution medium pH on SNAC solubility and precipitation (SNAC concentration = 75 mg/ml)				
Dilution medium	Concentration (mg/ml) (% starting SNAC)		precipitate (g) (% starting SNAC)	Supernatant pH *	Appear-ance
Original sol. (75mg SNAC/ml)	Sol 1 64.07 (100%) Sol 2 85.10 (100%)		n/a n/a	7.42	solution
0.1N HCl, pH 1.01	2 0.015ᵛ (0.1%)		1.879 (83.51%)	7.35 ± 0.15	precipitate
GIF pH 1.3 1	1 3.80 (22%) 2 2.95 (17%)		1.479 (65.73%)	7.15 ± 0.16	precipitate precipitate
PBS pH 6.2	1 0.58 (43%)		0.032 (1.42%)	6.09 ± 0.04	suspension
PBS pH 6.8	2 1.40 (80%)		n/d	6.51 ± 0.07	solution
PBS pH 7.4	2 1.16 (67%)		n/d	7.26 ± 0.05	solution

ᵛ Salicylic acid was detected in samples, 1 SNAC solution diluted is sol. 1; 2 SNAC solution diluted is sol. 2; * or the resulting solution in case of no precipitation; n/a not applicable; n/d not detected.

In the acidic environment of the simulated GIF or 0.1N HCl, (pH is below the salt's pKa) the SNAC in solution interact with the acid medium to form the less soluble free acid form of SNAC which would be precipitated from solution. The precipitation of SNAC acid from solution resulted in an increase in the solution pH and neutralisation of the solution. As the solution pH changed the equilibrium between ionised and non-ionised SNAC salt in solution would be readjusted accordingly and the solubility of the SNAC salt would increase.

-15-

The higher percentage of SNAC sodium remaining in solution for the solutions diluted with simulated GIF may be attributed to the presence of NaCl in GIF which provides additional Na⁺ counterions to keep SNAC in solution.
Higher concentrated SNAC solutions would increase the concentration of SNAC in the
5   diluted solution and therefore a greater degree of SNAC conversion to the free acid form and a higher increase in the pH of the resulting solution.

The white precipitate formed was not completely redissolved when diluted with phosphate buffer pH 6.2. However, clear solutions with no visual evidence of remaining precipitate were produced upon dilution with phosphate buffer, pH 6.8 and pH 7.4.
10   Individual results are shown in Table 1. Therefore it would appear that the SNAC free acid form produced in the acid medium of the stomach would start to redissolve upon leaving the stomach but would not be completely redissolved until it reaches the lower duodenum and jejunum.

DSC and XRD analysis identified the precipitate as the free acid form of SNAC.
15   DSC analysis of the precipitate displayed a sharp endotherm at 115°C which was similar to the endotherm previously known for the SNAC free acid form. The XRD pattern displayed by the precipitate was crystalline and similar to the XRD pattern recorded for crystalline SNAC acid. SEM analysis of the precipitate displayed orthorhombic crystals similar in shape to those previously observed for SNAC free acid.
20   The median particle size (D50%) and particle size distribution of the precipitate from the simulated GIF and the 0.1N HCl solution were similar, D50% of 31.87μm and 38.82μm respectively. SNAC precipitation in the in vitro medium studied did not result in the formation of colloidal/nanoparticles giving increased surface area for dissolution or absorption enhancement.

25   *Aqueous Heparin solutions containing 10,000IU, 30,000IU and 90,000IU Heparin in 30mls of 20% aq. PG*

An aqueous solution of PG containing Heparin without SNAC was investigated to assess the effect of the various pH environments on solutions with Heparin alone. Solutions containing a range of Heparin concentrations were added to simulated GIF.
30   The solution pH and Heparin concentration before and after dilution were determined as shown in Table 2. All the Heparin solutions were clear before and after dilution and

-16-

showed no sign of precipitation upon dilution. Greater than 100% Heparin activity was recovered when the Heparin solution with 90,000IU per 30ml was added to simulated GIF. There was a lower recovery of Heparin activity for the diluted Heparin solutions containing 10,000IU and 30,000IU per 30ml; however there was no precipitation observed.

Table 2: Heparin content in solution before and after dilution with simulated GIF (pH 1.3)					
Before dilution			After dilution		
Theoretical Heparin content IU/30mls (mg/ml)	pH	Actual Heparin content IU/mls	pH	Heparin content (IU/mls)	% Heparin in solution
10,000 (2.00)	7.5	257	1.89	60	78.00
30,000 (5.99)	7.1	979	1.69	181	78.43
90,000 (17.97)	6.7	2923	1.45	755	109.05

Due to the variability of the assay method used and the absence of a reduction in activity for the 90,000IU Heparin solution it was not possible to say whether the apparent reduction in Heparin activity in these diluted solution was real. Therefore, there was not sufficient evidence of a reduction in the in-vitro measured Heparin activity in these studies to suggest desulphonation of Heparin in the acid medium.

The pH of the Heparin starting solutions decreased as the level of Heparin in solution increased slightly. The Heparin sodium solutions examined did not display a strong neutralising capacity in the acidic gastric fluid, as did SNAC, nor did Heparin solubility appear to be effected the acidic medium. Therefore, it was concluded that solubility Heparin would not be influenced by the acidic stomach medium. However, the presence of Heparin in solution may influence the solubility of SNAC in gastric fluid by increasing the concentration of Na^+ counterions present.

Aqueous solutions of SNAC (75mg/ml) and Heparin (30,000IU and 90,000IU)

Aqueous PG solutions containing Heparin and SNAC were investigated to assess the effect of the various pH environments on solutions containing the combinations. The solutions analysed were 30ml in volume, containing 75mg/ml SNAC with 1,000IU/ml and 3,000IU/ml Heparin. A precipitate was formed when the solutions were diluted with simulated GIF. For the SNAC/Heparin solution with the lower level of

-17-

Heparin (1,000IU/ml) the presence of Heparin in solution did not influence the
neutralisation of GIF by SNAC sodium as shown in Table 1 and Table 3.

Table 3: Influence of dilution medium pH on SNAC solubility from a solution of SNAC 2.25g and Heparin 30,000 IU in 30mls of 20% aq. PG				
Dilution medium	solution assayed (mg/ml) (% starting SNAC)	precipitate (g) (% starting SNAC)	Supernatant pH *	Appearance
Original Solution	79.31 (100%)	-	7.61	solution
GIF pH 1.3	5.71 (33%)	1.637 (72.76%)	7.15	precipitate
PBS pH 6.2	0.63 (38%)	0.051 (2.27%)	6.14	suspension
PBS pH 7.4	2.02 (117%)	-	7.18	solution

* or of resulting solution in case of no precipitation

However, for the SNAC/Heparin solution with the higher level of Heparin
(3,000IU/ml) the neutralisation capacity of the SNAC in the diluted simulated GIF was
slightly reduced as shown in Tables 1 and 4. The slight reduction in the neutralisation
capacity of SNAC may be attributed to the increased concentration of Na^+ in solution
due to the Heparin concentration. At the lower concentration of Heparin this effect was
not evident.

Table 4: Influence of dilution medium pH on SNAC solubility from a solution of SNAC 2.25g and Heparin 90,000 IU in 30 mls of 20% aq. PG				
Dilution medium	solution (mg/ml) (% starting SNAC)	precipitate (g) (% starting SNAC)	Supernatant pH *	Appearance
Original Solution	106.03 (100%)	-	7.44	solution
GIF pH 1.3	1.12 (7%)	1.556 (69.93%)	6.81	precipitate
PBS pH 6.2	0.48 (28%)	n/d	6.10	suspension
PBS pH 7.4	1.73 (100%)	-	7.17	solution

* or of resulting solution in case of no precipitation; n/d not determined

The solubility of SNAC appeared to be influenced by the slight differences in pH
resulting from the different levels of Heparin in solution. As expected the percentage

-18-

SNAC in solution was higher in solutions with a more alkaline pH as shown in Table 3 and 4. The percentages of recovered precipitate were lower than expected for all SNAC solutions; this may be due to incomplete recovery of precipitate.

As for the previous SNAC solutions, the precipitate formed was partially
5   redissolved on dilution with phosphate buffer pH 6.2 and was completely redissolved upon dilution with phosphate buffer pH 7.4, Tables 3-4. In cases where the amount of SNAC measured in solution was greater than 100% this was attributed to the variability of the SNAC assay method. The Heparin content in these SNAC/Heparin solutions was measured before and after each dilution. From these results, shown in Table 5, there
10 was no obvious decrease in Heparin content in the diluted solutions. Fluctuations in measured Heparin concentrations were attributed to the variability of the assay method. Heparin solubility was not effected by the pH of the dilution medium or the presence of SNAC in the solution.

Table 5: Heparin in solution upon dilution of SNAC (75mg/ml) and Heparin solutions			
	% Heparin in solution (mg/ml)		
pH of dilution medium	GIF pH 1.3	PBS pH 6.2	PBS pH 7.4
SNAC 2.25g & Heparin 30,000 IU/30mls	88.83% (205 ± 4)	117.00% (27 ± 1)	99.67% (23 ± 1)
SNAC 2.25g & Heparin 90,000 IU/30mls	87.39% (605 ± 5)	91.00% (63 ± 6)	82.33% (57 ± 3)

15

DSC and XRD analysis identified the precipitate formed by the addition of the SNAC/Heparin solutions to the simulated GIF as the free acid form of SNAC. The DSC analysis of the precipitate displayed an endothermic peak, with an onset around 115°C similar to that of the SNAC free acid. The XRD patterns of the precipitates were similar
20 to that of SNAC free acid crystals. SEM analysis showed that the precipitate for SNAC/Heparin solutions was similar in shape to the precipitate formed from solutions of SNAC alone and the SNAC free acid crystals. There was no evidence of co-precipitate

-19-

formation between SNAC and Heparin. Particle size analysis of the precipitates showed that median particle size (D50%) of 30-64μm. Again, there was no evidence of the formation of colloidal/nanoparticles giving increased surface area for dissolution or absorption enhancement by precipitation of SNAC form solution in the acidic medium of the stomach.

Aqueous solutions with SNAC (150mg/ml) and Heparin in aq. PG

A solution containing Heparin (30,000IU in 70mls) and SNAC at a higher concentration and dose (150mg/ml or 10.5g in 70mls) was investigated to see the effect of increasing the dose and concentration of SNAC upon SNAC and Heparin solubility in different pH environments. When this solution was diluted with simulated GIF, a precipitate was formed. The pH of the supernatant formed was close to the pH of the original SNAC/Heparin solution, which indicated complete neutralisation of the simulated GIF by the SNAC/Heparin solution (Table 6).

Table 6: Influence of dilution medium pH on SNAC solubility from a solution of SNAC 10. 5g and Heparin 30,000 IU in 70 mls of 25% aq. PG				
Dilution medium	solution mg/ml (% starting SNAC)	precipitate g (% starting SNAC)	Supernatant pH *	Appearance
Original Solution	127.83 (100%)	-	7.83	solution
GIF pH 1.3	56.41 (91%)	1.796 (17.10%)	7.52	precipitate
PBS pH 6.2	2.08 (34%)	0.199 (1.90%)	6.19	suspension
PBS pH 7.4	5.58 (90%)	-	7.35	solution

* or of resulting solution in case of no precipitation

There was a large increase in the percentage of SNAC sodium remaining in solution after dilution compared to the corresponding SNAC/Heparin solutions containing 75mg/ml SNAC (Table 3). The concentration of SNAC remaining in solution was greater for the solutions diluted with the simulated GIF compared to the solutions diluted with 0.1N HCl due to the presence of NaCl in the simulated GIF. While the percentages of SNAC precipitated were greatly reduced compared to those solutions with a lower concentration of SNAC (75mg/ml), the mass of recovered precipitated SNAC was in the same range. The increase in the percentage SNAC remaining in solution was therefore attributed to the increase in the concentration and dose of SNAC

-20-

in the original solution. The increase in the concentration of SNAC results in a greatly degree of conversion of SNAC to the insoluble SNAC free acid form thus reducing the hydrogen ion concentration and causing an increase in pH to a more alkaline value close to than of the original solution at which the remaining SNAC stays in solution.

5   As for the previous SNAC/Heparin solutions, the precipitate formed upon dilution partially redissolved on further dilution with phosphate buffer pH 6.2 and was completely redissolved upon dilution with phosphate buffer pH 7.4 (Table 6). The Heparin content in these SNAC/Heparin solutions was measured before and after each dilution and showed little/no decrease in Heparin content in the diluted solutions. Percentages of
10   Heparin remaining in solution after dilution are listed in Table 7.

Table 7: Heparin in solution upon dilution of SNAC (150mg/ml) and Heparin solutions			
	% Heparin in solution (IU/ml)		
pH of dilution medium	GIF pH 1.3	PBS pH 6.2	PBS pH 7.4
SNAC 10.5g & Heparin 8,400 IU/70mls	70.93% (35.0)	97.14% (4.8)	87.02% (4.3)
SNAC 10.5g & Heparin 30,000 IU/70mls	119.57% (211 ± 23)	78.77% (14 ± 1)	85.00% (15 ± 1)

DSC and XRD analysis identified the precipitate as the free acid form of SNAC. The DSC analysis displayed an endothermic peak, with an onset around 115°C similar to that of the SNAC free acid. The XRD patterns of the precipitates were similar to the
15   SNAC free acid crystals. SEM analysis showed that the precipitate for SNAC/Heparin solutions was similar in shape to the precipitate formed from solutions of SNAC alone and the SNAC free acid. A median particle size (D50%) of 30-90 μm was measured for precipitate from solutions with 10.5g SNAC (150mg/ml) and Heparin in 70ml aq. PG. Once again there was no evidence of co-precipitate formation between the SNAC and
20   Heparin nor the formation of colloidal or nanoparticles upon precipitation.

-21-

Relationship between the in-vitro precipitation studies and the in-vivo biostudy results

The above in-vitro precipitation studies showed that a white precipitate was formed when SNAC and SNAC/Heparin solutions were diluted in an acidic dilution medium (simulated GIF or 0.1N HCl). The precipitate formed was characterised as the less soluble free acid form of SNAC. There was no evidence of SNAC/Heparin co-precipitation or microparticle formation and thus no suggestion of these mechanisms of Heparin absorption enhancement. The precipitate formed partially redissolved upon dilution with phosphate buffer pH 6.2 and completely redissolved when diluted with phosphate buffer pH 6.8 and 7.4.

There was no evidence pH effecting the solubility or activity of Heparin after in any of the SNAC/Heparin solutions studied. As the pH of the dilution media in this study were chosen to mimic the different pH environments in the gut, therefore, it can be concluded that SNAC will precipitate from the solutions studied in the low pH environment of the stomach and redissolve on exiting the stomach as it travels through the intestine from the duodenum to the ileum. The Heparin dosed would be expected to remain in solution throughout the GI tract.

There was a dramatic increase in the amount SNAC remaining in solution by increasing the concentration of SNAC in the dosing solution (from 75mg/ml to 150mg/ml) and the SNAC dose (from 2.25g to 10.5g). The quantity of SNAC precipitated appeared relatively constant (~1-2g) despite the SNAC dose administered. Previous biostudies were reviewed in light of the findings of these precipitation studies. As shown in Table 8, as the dose of Heparin increased the anti-factor Xa response increased.

Table 8: The Cmax and Tmax response to various treatments				
Treatment	SNAC (mg/ml)	Heparin (IU/ml)	C_{max} (IU/ml)	T_{max} (h)
B (30ml)	75	1,000	~	~
C (30ml)	75	2,000	0.103	2.5
D (30ml)	75	3,000	0.160	3.3
E (30ml)	75	5,000	0.210	2.4

-22-

The increased Heparin response can be attributed to the increased dose and concentration of Heparin in solution with SNAC.

In another biostudy, a higher dose of SNAC (10.5g) was dosed at a
concentration of 150mg/ml SNAC with doses of Heparin including a dose of 30,000IU Heparin. This dose of SNAC was higher than that required for therapeutic activity but dosed in a safety study. The increase in SNAC dose (compared to 2.25g SNAC administered as shown in Fig. 8) resulted a large increase in the APTT and anti-factor Xa activity. The higher Heparin activity was attributed to the increase in SNAC
concentration and dose. From the findings of the in-vitro precipitation studies, this increase may be attributed to the increase in the concentration of SNAC remaining in solution throughout the GI tract. There was no correlation was observed between the degree of SNAC precipitate and the level of Heparin response.

In the biostudy shown in Table 9, a range of SNAC/Heparin concentrations and
doses were investigated. Two equivalent doses of SNAC and Heparin at two PG concentrations were also compared.

Table 9: The C_{max} and T_{max} response to various treatments					
Treatment	SNAC (mg/ml)	Heparin (IU/ml)	% PG (g)	Anti-Xa activity (AUC)	Rank of C_{max} (Anti-Xa activity)
A (30ml)	75 (2.25g)	4,000 (120,000)	20 (6.00)	0.730	4
B (30ml)	75 (2.25g)	4,000 (120,000)	1 (0.30)	0.644	5
C (15ml)	150 (2.25g)	8,000 (120,000)	1 (0.15)	1.206	2
D (20ml)	150 (3.00g)	6,000 (120,000)	1 (0.20)	1.447	1
E (10ml)	150 (1.50g)	12,000 (120,000)	1 (0.10)	1.386	3

-23-

A number of factors were seen to influence the anti-factor Xa, C_{max} and AUC response for the treatments outlined in Table 9. An increase in PG concentration (treatment A compared to treatment B) resulted in an increased level of anti-Xa activity. The increased solubilising capacity of the solution due to the increased concentration of

5   PG may result in an increased level of SNAC remaining in solution on transit through the GI tract and this may result in an increased Heparin absorption. The comparison of treatments C, D and E showed that by maintaining the Heparin dose constant and by increasing the SNAC concentration and SNAC dose the level of anti-factor Xa response increased. Again the increased biostudy response was attributed to the increased

10   concentration and dose of SNAC remaining in solution on transit through the GI tract. Comparison of treatments B and C showed that the level of Heparin absorption was also considerably increased by delivering equivalent doses of SNAC and Heparin at different concentrations. Therefore, it was concluded that Heparin absorption was influenced by both the dose and concentration of SNAC and Heparin in solution

15   administered.

The findings of this precipitation study in combination with the results of a number of previous biostudies provide insight into the behaviour of the carrier/heparin solution on transit through the different pH environments of the GI tract and the effect of this behaviour on heparin/heparinoid absorption. The in-vitro studies of this example

20   show that SNAC is precipitated in the free acid at low pH and there is no evidence of co-precipitate formation between SNAC and heparin upon precipitation. The particle size of the precipitated SNAC was similar to that of the starting material and there was no evidence of microparticle/nanoparticle formation. The SNAC precipitate partially redissolved upon dilution with phosphate buffer (pH 6.2) and completely redissolved

25   when diluted with phosphate buffer at pH 6.8 and 7.4. It can be concluded, therefore, that SNAC will precipitate in the low pH environment of the stomach and that the precipitated carrier would redissolve on exiting the stomach as it travels through the intestine from the duodenum to the ileum. The heparin dosed remained in solution throughout the GI tract and was unaffected by the GI tract pH environments.

30   Various biostudies have shown that the heparin response is related to the level of heparin in solution and by increasing the concentration of heparin in solution the in-vivo heparin response increased. The heparin in-vivo response also increased by

-24-

increasing the level of SNAC in solution. By maintaining a constant dose of SNAC and heparin in solution and by increasing their concentration in solution there was a significant increase in the in-vivo heparin response.

From these results, it may be concluded that a molecular interaction between
5   SNAC and heparin in solution may be responsible for the enhancement in heparin absorption. The interaction between SNAC and heparin may occur in solution but not in the solid state upon precipitation. This may be explained by acidic conditions at which precipitation is seen and possible pH sensitivity of this molecular interaction which may only occur in the more alkaline environments of the GI tract. The extent of such an
10 interaction in solution would be dependent upon the concentration individual components in solution and thus explain the increase in the in-vivo response with an increase in the both SNAC and heparin dose and concentration in solution.

If such an interaction was responsible for the increase in heparin absorption, then the dosage form of the drug should be targeted at the lower GI tract (pH 6.8 - 7.4)
15 where the SNAC solubility in solution is optimum. The solid oral dosage forms according to this invention achieve this goal.

Example 2:   Formulation of SNAC/Heparin USP solid oral dosage forms using direct compression

SNAC sodium salt (lyophilised; Emisphere Technologies, Inc.) was milled prior
20 to tabletting in order to reduce particle size and size distribution and to improve its flow properties. Heparin sodium USP was supplied from Scientific Protein Laboratories containing 184.3 USP units per milligram. The mean particle size, D50%, of heparin and the milled SNAC particles were 122.37±28.76 μm and 49.68±8.9μm, respectively. The apparent density for both SNAC and heparin were measured and were similar at
25 0.5136gml^{-1} and 0.5416 gml^{-1} for heparin and SNAC respectively.

The milled lyophilised SNAC was used to prepare tablets containing 365mg SNAC to 150mg of Heparin per tablet; these tablets were designed so that three tablets would give the required dose of 1.1g of SNAC to 450mg of Heparin per dog. Tabletting was carried out using the Fette E1 single station tablet press (E3028) with a selection of
30 punches, such as 13mm round and 13X8mm oval punch. SNAC sodium and heparin

-25-

were blended with three other tablet excipients in the following composition as detailed in Table 10.

Table 10: SNAC/Heparin tablet blend			
Material	Per Unit % (w/w)/tab	mg/tab	per batch (g)
SNAC Sodium (milled)	63.13	365.75	180
Heparin Sodium	25.87	149.89	73.76
Explotab	10.0	57.936	28.51
Magnesium Stearate	0.5	2.89	1.42
Aerosil 200	0.5	2.89	1.42
Total Weight	100	579.356	285.11

5   Tabletting was carried out on the Fette E1 (E3028), using the 13mm round punches. The approximate die fill was 6mm, with a compression force of 42/3 and on target hardness of 50 - 70N. When heparin was included with SNAC, the compressibility of SNAC was compromised resulting in bigger tablets which were friable.

10   From the 420 tablets that were made, approximately 100 tablets were retained uncoated, for release testing such as potency testing, disintegration and dissolution and for dosing in the biostudy. The remaining tablets were weighed and were coated with Eudragit S enteric coating using the Hi coata.

Coating of the SNAC/Heparin tablets was carried out to a tablet weight gain of
15   approximately 5%. The tablet size and shape coated easily; however, the original tablets (uncoated) were friable and after coating with Eudragit S, cracks were seen to develop on the surface and on the edges of the tablets. A Eudragit S coating solution was made containing 9.98% solids in solution calculated from the material listed in Table 11.

20

Table 11: Composition of Eudragit S coating solution		
Material	**Per Batch (g)**	**Actual Used (g)**
Eudragit S12.5	0.9976	0.99812
Diethyl Phthalate	0.0252	0.02540
Isopropyl Alcohol	0.8666	0.86674
Water	0.0612	0.06132
Talc	0.0492	0.04950
Total Weight	2.0000	2.00108

The water, isopropyl alcohol and diethyl phthalate were added to a stainless steel vessel and the mixer was switched on at 100rpm for 15 minutes to ensure that a uniform solution was obtained. Eudragit S12.5 was added gradually to the solvent

5   mixture and mixing was continued for a further 10 minutes at a speed of 125rpm. Talc was then added to the solvent mixture and the mixing was continued for a further 20 minutes at 150 rpm.

The tablets, both coated and uncoated, were assayed for potency of SNAC and heparin (n =6). The disintegration of tablets was monitored in water at 37°C. The

10   uncoated tablets were found to disintegrate within 5 minutes in water at 37°C, while the coated tablets did not disintegrate within the first 30 minutes but had fully disintegrated after 2 hours in water at 37°C.

Dissolution testing was carried out at both pH 1.2 and pH 7.4. Both SNAC and heparin release were monitored. For the uncoated tablets, heparin release was faster

15   than SNAC release at pH 1.2, with 54% of Heparin released after 15 minutes and up to 94% released after 1 hour compared with 16% of SNAC released after 15 mins and up to 19% released after 1 hour. The release of Heparin and SNAC was similar at pH 7.4 with 82% heparin released compared to 76% of SNAC after 15 minutes. Heparin release at pH 1.2 was slower than that at pH 7.4, especially at the early time points of

20   15 mins and 30 mins. For SNAC, release at pH 1.2 was very slow with only 19% release after 1 hour. SNAC release was complete after 1 hour.

-27-

For coated tablets, heparin *in vitro* release was low (<10%) at pH 1.2 after 2 hours while no SNAC was detectable at pH1.2 during the two hour dissolution. At pH 7.4, the release of heparin was higher than SNAC at the early time point of 15 mins with 33% of Heparin released and 18% of SNAC released after 15 mins. After 2 hours

5   dissolution, the release of Heparin was complete and SNAC release was nearly complete at 90%. Neither SNAC and heparin were released at pH 1.2 but both were released at pH 7.4 showing that the enteric coating was effective.

Example 3:   Formulation of SNAC/Heparin USP solid oral dosage forms using
10   **aqueous granulation**

Granulation was investigated to improve the particle size, flow properties, density compressibility of the SNAC/Heparin material and ultimately allow the production of good quality SNAC/Heparin tablets. SNAC and SNAC/Heparin granules were produced by aqueous granulation. The effect of the inclusion of intragranular and

15   extragranular tabletting excipients, Explotab, Methocel, Avicel and Kollidon, was investigated. The SNAC/Heparin ratios in the granules investigated were 2.25g SNAC to 90,000 IU Heparin and 2.25g SNAC to 150,000 IU Heparin which were equivalent to the concentrations in the taste-masked solutions used for dosing in man. Granule yield, density, flow properties and water content were measured and selected granular

20   material was tabletted. Aqueous granulation of SNAC and Heparin prior to tabletting enabled SNAC:Heparin tablets of good quality to be produced.

Granules and tablets were assayed for SNAC potency, SNAC release at pH 1.2 and 7.4 and residual moisture content. Heparin potency and Heparin release at pH 1.2 and 7.4 was also determined for the SNAC:Heparin tablets. Disintegration testing of the

25   tablets was also carried out in water at 37°C.

SNAC sodium salt (triturated) and the dry granule excipients were blended in a Kenwood mixer low speed for 1-2 minutes prior to the addition of the granulating liquid. The granulating liquid was added slowly and dispersed well in the granular mix until the granulation endpoint was achieved. The granular material was sieved through a

30   1.40mm sieve or a 1.18mm sieve and the resulting granules were dried overnight at 60°C (except where otherwise stated). The dried material was sieved through a 355 µm

-28-

sieve to separate fine material from the granules. The sieve apertures selected were larger that those normally used in granulation (0.315mm) to facilitate the manual sieving of the granular material.

The aerosil 200 was bag blended with the SNAC granules or the SNAC:Heparin
5   granules, the magnesium stearate was then added and bag blended. The tablet weight was set at approximately 500mg and the tablet hardness was set as reported. Tabletting was carried out on the Manesty E2 single station using the 12mm round punch and die set.

SNAC analysis was carried out using a HPLC method as described in Example
10   1. SNAC and Heparin potency of the granules and tablets were measured. Dissolution testing of SNAC and Heparin from granules and tablets was undertaken at 37°C in simulated gastric fluid pH 1.2 and isotonic phosphate buffer pH 7.4. Disintegration testing of tablets was measured in water at 37°C. Karl Fisher titration was used to determine percentage water content in the granules and tablets. Heparin molecular
15   weight was determined by aqueous Gel Permeation Chromatography (GPC) analysis. Differential Scanning Calorimetry (DSC) was conducted using a Perkin Elmer 7 Series thermal analysis systems.

Granulation of SNAC sodium

The granulation of pure SNAC sodium was investigated with and without the
20   inclusion of PVP as a binding agent. A binder, PVP 26-28 was added to the granulate mix as a 10% aqueous PVP solution and as a dry powder. The formulation of these granules is outlined in Table 12.

The SNAC sodium granules Batch 1 prepared by adding PVP solution to the granular material did not granulate well. The granulating liquid was poorly dispersed
25   through the granular mix and hard granules were formed. Overwetting the granular mixture can also result in granule hardness. The Batch 2 granules were prepared by blending PVP as a dry powder with the SNAC sodium powder prior to the addition of the granulating liquid. The volume of granulating liquid was also reduced in an attempt to reduce granule hardness but hard granules were still produced. The SNAC granules
30   Batch 4 produced without the inclusion of PVP were also hard. Granule hardness may

-29-

be due to the solubility of SNAC in the granulation fluid. Strong bonds may form as a result of fusion or recrystallisation of SNAC particles upon drying. Because addition of the binder PVP would further increase granule cohesive forces and granule hardness, a binder was omitted from the granular formulation.

Table 12: Formulation of SNAC granules				
Granulate Batch	1	2	3	4
Granulate formulation	%	%	%	%
SNAC	100	97	90	100
PVPK 26-28	-	3	-	-
PVPK 26-28 (10%)ml	50	-	-	-
Explotab	-	-	10	-
Water (ml/100g)	-	30 ml	50 ml	50 ml
Batch size (g)	100	100	66	100

A tablet disintegrant, 10% Explotab, was added to the granular mix Batch 3 in an attempt to dilute the cohesive forces between the particles in the SNAC granules and hence to decrease the SNAC granule hardness. The granules produced displayed reduced hardness. The flow properties, angle of repose and compressibility index of these granules indicated good granular flow. The apparent density of Batch 3 granules (0.4381g/ml) was greater than the triturated SNAC sodium starting material (0.2451g/ml). Therefore, these SNAC granules were expected to exhibit better compressibility than the SNAC starting material and hence to produce less friable tablets. The Batch 3 granules were tabletted to produce SNAC tablets.

Granulation of SNAC:Heparin for inclusion in SNAC:Heparin IR tablets

SNAC:Heparin granules were prepared for inclusion in SNAC:Heparin IR tablets. The ratios of SNAC sodium to Heparin in the granules prepared were 2.25g SNAC sodium to 90,000IU Heparin (Table 13) and 2.25g SNAC sodium to 150,000IU Heparin (Table 14). Explotab was added to each of the granular mixes to reduce granular hardness. The SNAC:Heparin granules prepared with 7.45% Explotab (Batch 5 and Batch 6) were very hard. The increased hardness of the Hardness was reduced in the

-30-

Batch 7 granules by increasing the percentage Explotab in the granular mix from 7.45% to 9.09%. The Batch 7 granules exhibited good flow properties. The apparent density of the SNAC/Heparin granules was not effected by the presence of Heparin. In an attempt to reduce the granular water content. Batch 8 granules were prepared using a 1:1 water/ethanol granulating liquid. However, a greater volume of granulating fluid was required to reach the granulation endpoint and the water content in the dried Batch 8 granules was still high (14.93%).

Table 13: Formulation and characteristics of granules with a ratio of 2.25g SNAC sodium to 90,000IU Heparin				
Granulate Batch	5	6	7	8
	%	%	%	%
SNAC-Sodium	74.7	74.7	73.37	73.37
Heparin-USP	17.85	17.85	17.54	17.54
Explotab	7.45	7.45	9.09	9.09
Water	40 ml	50 ml	50 ml	37.5 ml
EtOH	-	-	-	37.5 ml
Apparent density (g/ml)	-	-	0.4423±0.007	-

The granules with a ratio 2.25g SNAC to 150,000 IU Heparin required a lower level of water to reach the granulation endpoint point (Table 14) compared to the granules with a ratio of 2.25g SNAC to 90,000 IU Heparin (Table 13). The reduced level of water may be due to the reduced proportion of hygroscopic SNAC in the granular mix. These granules (Batches 9, 10 and 11) exhibited good flow properties and apparent densities greater than the SNAC starting material.

Table 14: Formulation and characteristics of granules with a ratio of 2.25g SNAC sodium to 150,000IU Heparin					
Granulate Batch	9	10	11	12	13
	%	%	%		
SNAC-Sodium	67.73	67.73	68.26	65.97	62.3
Heparin-USP	23.16	23.18	24.74	24.03	22.7
Explotab (%)	9.09	9.09	7.0	7.0	-
Water per 100g batch	36 ml	32 ml	35ml	23	31
Kollidon 30				3.0	
Avicel pH101					14
Apparent density (g/ml)	-	0.4639 ±0.013	0.4861 ±0.030	0.4899 ± 0.005	0.4440 ± 0.006

To optimise the SNAC/Heparin granules with a ratio of 2.25g SNAC to 150,000IU Heparin a number of excipients i.e. Explotab, PVP 30 and Avicel pH101 were added to the granular mix. Although Explotab and PVP 30 had been used in previous granular mixes as binder and diluent/disintegrant respectively, a combination of Explotab and Kollidon 30 in the granular mix was investigated (Batch 12). The inclusion of Avicel pH101, which acts as a diluent but also a lubricant and disintegrant, was examined in the granular mix (Batch 13). The formulation and characteristics of these granules are summarised in Table 14.

Batch 7, Batch 10, Batch 11, Batch 12 and Batch 13 SNAC:Heparin granules were selected for the inclusion in SNAC:Heparin IR tablets.

Granulation of SNAC:Heparin for inclusion into SNAC:Heparin SR tablets

The formulation of SNAC:Heparin granules with Hydroxypropyl methyl cellulose, Methocel, a water soluble polymer was selected as the controlled release component of these tablets. Methocel partially hydrates upon contact with an aqueous medium to form a gel layer which controls the rate of release of drug from the tablet by a diffusion and/or erosion mechanism. The rate of release of the drug can be varied by varying the grade of Methocel used. One group of these polymers, Methocel K100LV was selected for inclusion in the formulation of SNAC:Heparin granules. The formulation details are listed in Table 15.

-32-

Table 15: Formulation and characterisation of the SNAC:Heparin granules with Methocel	
Granulate Batch	**14**
Granulate formulation SNAC Sodium Heparin Methocel K100LV	% 62.30 22.1 15.0
Water (ml)	25
Apparent density (g/ml)	0.4270 ± 0.0066

The flow properties of these granules were good. The apparent density of the granules was similar to the other SNAC:Heparin granules and was greater than the SNAC starting material. The percentage fine material retrieved for these granules was high
5   (40%). SR tablets were prepared from the Batch 14TEXP1767 granules.

Tabletting of SNAC Sodium IR granules

Formulation of the SNAC sodium tablets prepared from SNAC Batch 3 is shown in Table 16. The tablet blend compressed well and the resulting tablets were smooth and showed no sign of capping or chipping.

Table 16: Formulation of SNAC tablet blend	
Tablet No.	**A**
Granulate Batch No.	**3**
Tablet formulation Granulate Explotab Mag. Stearate Aerosil 200	% 99.0 - 0.5 0.5
Tablet weight	500mg

10

Formulation of SNAC:Heparin IR Tablets

SNAC:Heparin IR tablets were prepared with a ratio of 2.25g SNAC sodium to 90,000IU Heparin from the Batch 9 granules and with a ratio of 2.25g

-33-

SNAC sodium to 150,000IU Heparin from the Batch 10 and Batch 11 granules. The formulation of the tablets are summarised in Table 17.

Table 17: Formulation of SNAC:Heparin tablet blends					
Tablet No.	B	C	D	E	F
Granulate Batch	7	10	11	12	13
SNAC per 500mg Heparin per per 500mg	361.18mg 16,000 IU	368.78mg 25,107I U	310.59mg 20,745IU	300.15mg 20,151IU	261.66mg 17,571IU
Tablet formulation	%	%	%	%	%
Granulate	99.0	99.0	91.0	91	84
Explotab	-	-	8.0	8	15
Mag. Stearate	0.5	0.5	0.5	0.5	0.5
Aerosil 200	0.5	0.5	0.5	0.5	0.5
Tablet weight	500mg	500mg	500mg	522mg	479.5mg

Formulation of SNAC:Heparin SR Tablets

5   SNAC:Heparin SR tablets were prepared by compression of granules containing an SR component Methocel (Batch 14). SR tablets were also prepared using IR granulates (Batch 11) and adding Methocel K100LV to the tablet blend, extragranularly as shown in Table 18.

Table 18: Formulation of the SNAC:Heparin SR tablet blends		
Tablet No.	G	H
Granulate Batch	11	14
Theoretical SNAC per 500mg Theoretical Heparin per 500mg	286.7mg 18,890 IU	277.24mg 18,525 IU
Granulate	84.0	89.0
MethocelK100LV	15.0	-
Explotab	-	10
Mag. Stearate	0.5	0.5
Aerosil 200	0.5	0.5
Tablet Weight	515mg	520mg

-34-

Dissolution testing: All the granules tested displayed 100% SNAC release at the 30 minute time point in a dissolution medium of pH 7.4. The SNAC release was greatly reduced in the dissolution medium of pH 1.2, less than ≤ 14% SNAC was released after 2 hours of testing. The presence of Kollidon 30 and Avicel did not influence SNAC

5   release from the Batch 12 and 13 granules. The SNAC release profiles from these IR tablets were similar to the SNAC release profiles from the uncoated IR tablets of Example 2. The presence of the SR component in the Batch 14 granular mixture did not influence the release of SNAC from these granules.

Molecular weight of Heparin in granules: The average molecular weight (Mw)

10   and the number average molecular weight (Mn) of Heparin in granules with a 2.25g SNAC to Heparin 90,000 ratio (Batch 7) and 2.25g SNAC to Heparin 150,000 ratio (Batch 10) was determined and compared to the Heparin starting material. Mw, Mp and Mn values of Heparin present in the SNAC:Heparin granules (Batch 7 and Batch 10) were slightly greater than for the Heparin reference material as shown in Table 19. The

15   increased Heparin molecular weight during the granulation process may be a result of a complex formation with one of the components in the granular mix.

Table 19: Molecular weight distribution of Heparin in SNAC:Heparin granules			
Batch	Ref. Hep. USP	Batch 7	Batch 10
Mw (Daltons)	11273 ± 45	11738 ± 110	11661 ± 50
Mn (Daltons)	9694 ± 40	10429 ± 161	10248 ± 37
Mp (Daltons)	12358 ± 91	12424 ± 426	12615 ± 96
Polydispersity	1.1628 ± 0.0014	1.1256 ± 0.0070	1.1378 ± 0.0014

Dissolution testing: The SNAC release from Tablets B, C and D was ≥ 100% at the 30 minute time point in pH 7.4. The presence of the SR component

20   MethocelK100LV both extragranularly (Tablet G) and intragranularly (Tablet H) influenced the SNAC release from the SNAC/Heparin tablets in pH 7.4. The Tablet G release profile showed 90% release at 30 minutes which increased to 110%, at the 2 hour time point. The Tablet H tablets displayed a gradual release of SNAC with 100% release around the 4 hour time point as shown in Figure 1. The SNAC release was

25   reduced for the tablets tested in a dissolution medium of pH 1.2. The release of SNAC

-35-

from the IR (Tablet D) and SR tablets (Tablet H) in this study was similar to the release from the uncoated SNAC/Heparin tablets described in Example 2 and dosed in the dog biostudy. The poor dissolution of SNAC from the SNAC/Heparin tablets and granules at pH 1.2 can the related to the poor solubility of SNAC sodium at low pH.

5   The Heparin release from the IR tablets (Tablet H) reached 80% at 30 minutes in a dissolution medium of pH 7.4, and fluctuated around this level over the 4 hour testing period. The 80% level of Heparin released may be due to the variability of the assay method rather than incomplete release of Heparin from the IR tablet. Two other batches of IR tablets tested (Tablets B and C) displayed 100% Heparin release after 30
10   minutes at pH 7.4. The SR tablets displayed a sustained release profile with the Tablet H tablets giving a more gradual release profile for Heparin than the Tablet G tablets. At pH 7.4, the Tablet H tablets released SNAC and Heparin gradually over a 4 hour period with the release of Heparin being faster as shown in Figures 1 and 2.

          The Heparin release from the IR tablets (Tablet D) and SR tablets (Tablet G) in
15   the dissolution medium of pH 1.2 was low < 40% release over a 4 hour period. The presence of an intragranular SR component in Tablet H tablets suppressed Heparin release at pH 1.2 with approximately 6% Heparin released after 4 hours of testing.

          The release profiles of SNAC and Heparin from the IR tablets at pH 7.4 were similar to those of the uncoated IR tablets dosed in the Dog Biostudy (Examples 2 and
20   4 herein). The Heparin release from the IR tablets prepared in this study at pH 1.2 was approximately 40% after 4 hours compared to 100% release from the uncoated IR tablets dosed in the Dog Biostudy after 2 hours. The difference in the level of Heparin release from the IR tablets prepared in this study and the biostudy uncoated IR tablets may be due to the method of tablet manufacture, the material used in tablet
25   manufacture and the quality of the tablets produced. The biostudy IR tablets (Example 2 herein) produced by direct compression were friable. The tablets produced by aqueous granulation compressed well to give smooth shiny tablets. The aqueous granulation process would produce a more intimate mixture of Heparin with SNAC than direct compression. Therefore, the retarded release of Heparin from the IR tablets at
30   pH 1.2 may be due to the hydrophobic nature of SNAC at pH 1.2 preventing the dissolution of Heparin from the tablet matrix. The uncoated IR tablets dosed in the dog

-36-

biostudy were friable and therefore Heparin contact with the dissolution medium would be increased allowing 100% Heparin release at 2 hours. The reduced Heparin release at pH 1.2, may also be due to possible complex formation between Heparin and one of the components in the granular mix as indicated by molecular weight gain in the GPC analysis which reduced the Heparin dissolution rate at pH 1.2.

Example 4: **Administration of SNAC/Heparin USP solid oral dosage forms to dogs**

A biostudy was undertaken in dogs (beagles; n=6) to compare the performance of SNAC/Heparin tablets formed by direct compression as described in Example 2, either uncoated or coated with an enteric coat (Eudragit S), to a 20% propylene glycol solution of SNAC/Heparin and an aqueous solution of SNAC/Heparin that did not contain any propylene glycol. The dogs were each orally administered 1.1 g of SNAC and 450 mg of heparin as three tablets or 7.3 ml of solution as follows:

Uncoated tablets   (450 mg heparin + 1.1 g SNAC, oral (3 tablets)

Coated tablets   (450 mg heparin + 1.1g SNAC, oral (3 tablets)

PG solution   (450 mg heparin + 1.1 g SNAC +20% PG, oral, 7.5ml)

Solution   (450 mg heparin + 1.1 g SNAC, oral, 7.5ml)

The mean anti-Xa Activity Data measured over 5 hours is shown in Figure 3 and Table 20 provides a summary of the pharmacokinetic parameters for anti-Xa Activity data following oral administration of the first three formulations.

Table 20: Pharmacokinetic parameters for dog biostudy				
	Cmax (IU/ml)	Tmax (h)	$AUC_{0.5}$ (IU h ml^{-1})	F (relative bioavailability)	F* (calculated using APTT data)
Uncoated	0.14 ±0.09	0.93±0.85	0.292±0.11	1.00±0.64	0.63±0.39
Coated	0.28±0.30	2.08±1.02	0.49±0.47	1.39±1.41	1.23±1.07
Solution with PG	0.23±0.14	0.50±0.31	0.25±0.16	1	1

-37-

The APTT response was low in all the studied legs with a delay in Xa and APTT response following administration of coated tablets in comparison to the uncoated tablets and the solution formulation. Comparable areas under the plasma heparin concentration versus time curves were achieved for the uncoated tablets and the two dosing solutions. In contrast, the enteric coated tablets yielded about twice the AUC of the other groups. It may be that maintaining the SNAC and heparin in physical proximity prior to entry into the intestine (targeting the SNAC and heparin to the lower GI tract) was beneficial in this respect.

Example 5: *Formulation of SNAD/Heparin USP solid oral dosage forms using aqueous granulation*

Preformulation studies of SNAD show that SNAD is microcrystalline in nature with poor flow properties. Thus, SNAD and SNAD/Heparin granules were prepared to assess the suitability of the SNAD material for aqueous granulation with and without excipients. The granule formulation details are detailed in Table 21.

Table 21: Composition of SNAD and SNAD/Heparin granules						
Granule Batch	**16**	**17**	**18**	**19**	**20**	**21**
SNAD	100%	63.31%	61.41%	47.49%	50.65%	44.32%
Heparin	-	36.69%	35.59%	27.51%	29.35%	25.68%
PVP (k30)	-	-	3%	-	-	-
Methocel K100LV	-	-	-	-	20%	20%
Avicel PH102	-	-	-	20%	-	10%
Explotab	-	-	-	5%	-	-
Water (ml)	9.5	19	16.5	13	21	15

The SNAD material alone granulated well. The addition of Heparin to the granule blend increased in the amount of water required to reach the granulation endpoint. A binder PVP was added to the SNAD/Heparin granule mix in an attempt to reduce the amount of water required to reach the granulation endpoint and hence soften granules. The addition of the PVP to the granular mix did reduce the volume of water required, however, there was no evident improvement in granular quality.

-38-

Avicel and Explotab were added to the SNAD/Heparin granules to reduce granule hardness. Avicel was the selected diluent due to its poor aqueous solubility which was hoped to reduce the formation of crystalline solid bridges on drying and soften the granules. Explotab was added to the granule to aid disintegration of the

5   granules in the dissolution medium. The volume of water required to reach the granulation endpoint was reduced but otherwise there was no evident difference in granule quality or yield.

A SR component, Methocel K100LV, was added to the SNAD/Heparin granules to obtain a gradual release of SNAD and Heparin from the granules. The amount of

10   water required to reach the granulation endpoint was increased possibly due to hydration of the Methocel during granulation and yield achieved was similar to that obtained for the IR granulates. Avicel was added to the granular blend as a diluent to reduce granule hardness. Avicel was selected due to its poor aqueous solubility which would reduce the formation of solid bridges and maintain the inherent SR

15   characteristics of Methocel (hydration and gel formation) which can be undermined by water soluble excipients. The addition of Avicel to the granules did decrease the volume of water required to reach the granulation end point and the hardness of the granules produced. However the total yield of granules was reduced.

Formulation and Development of SNAD/Heparin Tablets

20   The batches 16 to 21 of SNAD and SNAD/Heparin granules were tabletted with a range of excipients to assess their compressibility and processability. SNAD and SNAD/Heparin tablet formulations are detailed in Table 22.

SNAD/Heparin tablet blends were prepared SNAD/Heparin granules and 0.5% Mag. Stearate and with 4% Explotab and 15% Pharmatose. Both blends produced

25   good quality tablets of adequate tablet hardness. The level of external lubricant appeared to be insufficient and tablets adhered to the lower punch during manufacture. Tablets blends were also prepared from SNAD/Heparin granules with 5% Explotab intragranularly and 0.5% Mag.Stearate. There were no problems noted while tabletting the blend and no sticking to the lower punch was noted. The improved lubrication of

30   this blend was attributed to the higher percentage of excipients in the table blend.

Table 22: Composition of SNAD and SNAD/Heparin Tablets							
Table Lot	I	J	K	L	M	N	O
Granule batch Granule %	16 99.5%	17 99.5%	17 84.58%	20 99.5%	21 99.5%	21 84.58%	19 94.5%
Magnesium Stearate	0.5%	0.5%	0.43%	0.5%	0.5%	0.45%	0.5%
Pharmatose DC11	-	-	15%	-	-	-	-
Explotab	-	-	4%	-	-	-	5%
Methocel K100LV	-	-	-	-	-	10%	-
Tablet weight (mg)	234.7 ± 4.3	324.4 ± 9.7	347.2 ± 12.2	295.4 ± 5.5	290.8 ± 10.7	295.4 ± 8.9	299.4 ± 15.7

The disintegration times were measured for tablets without a disintegrant and with Explotab intra and intergranularly. The disintegration times were similar for the three tablet batches between 13-15 minutes.

SNAD/Heparin granules containing Methocel were tabletted with 0.5% Mag. Stearate. A second batch of SNAD/Heparin granules containing Methocel and Avicel intragranularly with 0.5% Mag. Stearate and with extra 10% Methocel intergranularly were tabletted. Good quality tablets were produced with no evidence of sticking to the punches during manufacture, as was observed for batches of IR tablets. The addition of Methocel to the granules reduced the granule tackiness upon compression.

The disintegration times for these tablets were considerably longer than the IR formulations as was expected for a SR formulation. The addition of 10% Avicel to the granules further increased the tablet disintegration time. A further increase in disintegration time was observed with the addition of intergranular Methocel to the formulation.

-40-

Manufacture of SNAD/Heparin IR tablets for In-Vivo testing

The following SNAD/Heparin prototypes selected for a Dog Biostudy:

SNAD/Heparin IR tablets (uncoated)

. SNAD/Heparin IR tablets (coated with Eudragit S)

5   SNAD/Heparin IR tablets (coated with Eudragit L)

These tablets were designed to deliver a dose of 90,000IU (419mg) Heparin and 550mg SNAD in two tablets. Two grades of enteric coating, Eudragit S and L, were selected. These anionic acrylic polymers resist dissolution at acidic pHs and dissolve in alkaline media. The pH at which they dissolve is dependent on the degree of

10   Methacrylic acid substitution; Eudragit L dissolves at pH6 and Eudragit S at pH7. Therefore, tablets coated with Eudragit L will dissolve in the upper intestine while tablets coated with Eudragit S will dissolve along the GI tract.

Manufacture of SNAD/Heparin USP IR tablet cores

A batch of SNAD granules and SNAD/Heparin granules (ratio 550mg SNAD:

15   90,000IU Heparin) were produced. Formulation and yield details are listed in Table 23.

Table 23: Composition of SNAC and SNAD/Heparin granules		
Granule Batch	22	23
SNAD	100%	45.40%
Heparin	-	34.60%
Avicel PH102	-	20%
Batch size (g)	500g	600g
Water (ml)	68ml	130ml

In-process analysis of the SNAD/Heparin granules showed the SNAD potency of the granules lower than expected, 96.8% label claim and the Heparin was superpotent in the granules i.e. 107.4%. In order to obtain the desired ratio of SNAD to Heparin

20   (550mg SNAD: 90,000IU Heparin) in the final tablets, SNAD granules were added to the tablet blend. A tablet blend composition is detailed in Table 24 (*in vitro* dissolution profile for this composition is given in Figure 4). Good qualitity tablets were produced.

Table 24: Composition of SNAD/Heparin IR tablets	
Tablet lot	P
SNAD/Heparin Batch 23	86.45%
SNAD granules Batch 22	4.55%
Explotab	8%
Mag. Stearate	0.5%
Aerosil	0.5%
Tablet weight	657mg

The SNAD/Heparin IR tablets (Tablet P) were coated with Eudragit S and Eudragit L enteric coatings. The coating solution used was an organic solution and the formulation details are given in Table 25:

Table 25: Composition of coating solution			
Coated Tablet 1	Kg/per Litre	Coated Tablet 2	Kg/per Litre
Eudragit S12.5	0.4986	Eudragit L12.5	0.4986
Diethyl Phthalate	0.0126	Diethyl Phthalate	0.0126
Talc	0.0246	Talc	0.0246
Isopropyl alcohol	0.4333	Isopropyl alcohol	0.4333
Water (ml)	0.0306	Water (ml)	0.0306

5   Disintegration: Uncoated IR tablets (Tablet P) completely disintegrated in 12min 25sec (± 13sec). Both batches of enteric coated tablets resisted disintegration at pH1.2. At pH7.4 a lag time was observed prior to the start of disintegration. The lag time was longer for the Eudragit S coated compared to the Eudragit L coated tablets. The total time from introduction into pH7.4 buffer to complete disintegration was 46mins

10   48secs for the Eudragit S coated tablets and 22mins 8secs for the Eudragit L coated tablets. The disintegration time of the tablets coated with Eudragit L was shorter than those coated with Eudragit S due to the faster dissolution of Eudragit L coating at pH7.4.

Dissolution studies: SNAD and Heparin showed parallel release from the

15   uncoated IR tablets in a pH7.4 dissolution medium. Near complete release of both SNAD and Heparin was measured after one hour as is shown in Figure 4 for Tablet P.

-42-

Heparin is highly soluble (~600mg/ml) and appears to have a fast dissolution rate. The saturated solubility of SNAD is relatively high (~359mg/ml), however, it appears to have a low intrinsic dissolution rate resulting in a slower release profile than expected for these IR tablets. An intimate mixture of SNAD and Heparin material may be formed by aqueous granulation and the Heparin release from these tablets may be limited by the slow dissolution of the SNAD material due to this intimate mixture.

At pH 1.2, SNAD release from the tablets was negligible (<0.5% release). Less than 20% Heparin was released after one hour. Heparin is highly soluble at pH 1.2 and the SNAD sodium salt is converted to an insoluble free acid form in the acidic medium. The dissolution of Heparin at this pH is limited by the enteric effect of the SNAD material.

The SNAD and Heparin release at pH7.4 were comparable to the release profiles for the SNAC Heparin tablets (Example 2) dosed in previous dog biostudy (Example 4). These SNAC/Heparin tablets were produced by direct compression. The release of SNAC at pH1.2 was greater than that of the SNAD material and Heparin release was higher from the SNAC/Heparin tablets possibly due to the extra granulation step in these tablets and the poorer dissolution rate of the SNAD material.

Example 6:   Formulation of SNAD/LMWH solid oral dosage forms using aqueous granulation

SNAD was supplied by Emisphere Technologies Ltd and Low Molecular Weight Heparin (LMWH or LMW heparin) was supplied by Parnaparin (potency 91IU/mg). SNAD analysis was carried out using a HPLC method and LWMH analysis was carried out using and anti-FXa assay kit, , Coatest® supplied by Chromogenix.

Granulation was SNAD with LMWH was investigated in the absence and presence of excipients as shown in Table 26, including the presence of a wetting agent (SLS). Batches 24-27 produced large quantities of hard granules. The size distribution of Batch 28 granules was much improved with a much higher % of granules less than 355μm.

Table 26: SNAD/LMWH granules					
Batch No.:	24	25	26	27	28
E597	35.74	28.59	32.88	33.67	32.13
LMWH	64.26	51.41	59.12	61.23	57.77
Explotab	-	5	5	5	10
SLS				0.1	0.1
PVP	-	- .	3		
dH$_2$O	14ml	12ml	13ml	20ml	10
Avicel	-	15	-		

Tablets were prepared from the granules produced in above. The required amounts of Explotab, Aerosil and magnesium stearate as shown in Table 27 were bag

5   blended and tablets were produced on a Manesty hand operated tablet press using 12.5mm round punches.

Table 27: SNAD/LMWH Tablet Blends				
Granulate Batch No.:	24	25	26	27
Tablet Lot No.:	Q	R	S	T
Formulation	%	%	%	%
Explotab/mg stearate/ aerosil blend	6	6	6	6
E597	33.60	26.87	30.90	31.65
LMWH	60.40	48.33	55.57	57.56
Explotab	-	4.7	4.7	4.7
PVP	-	-	2.82	-
SLS	-	-	-	0.094
Avicel	-	14.1	-	-
Target tablet weight (mg)	546	682	593	579

SNAD : LMWH tablets were formulated for use in the dog biostudy of Example 7

10   for determination of the pharmacokinetics of LMWH in dogs. Two strengths of tablets were prepared with ratios of SNAD : LMWH of 550mg : 90, 000IU and 1100mg : 90,000IU. The tablets containing the higher strength of SNAD was formulated as a three tablet dose, while the tablets containing the lower strength of SNAD were formulated as a two tablet dose.

-44-

The SNAD (1100mg):LMWH (90,000IU) granules were formulated at 499.7mg/g SNAD, 449.3 mg/g LMWH, 50.0 mg/g Explotab, and 1.0 mg/g SLS for a total weight per unit of 1000 mg. SNAD, LMWH and Explotab were bag blended for 3 minutes and transferred to a Kenwood mixer. The SLS was dissolved in 5mls of deionised water and

5   this was added to the Kenwood using a syringe. Deionised H_2O was subsequently added until the granulation end-point was reached (total 32mls). The granulate was transferred to an oven and tray dried for 16 hours at 70°C. The granulate was weighed after drying and passed through a 630µm sieve on an oscillating granulator. Granule flow properties were assessed to determine the suitability of the granules for tabletting.

10   The granules were analysed for SNAD and LMWH potency content.

The SNAD (550mg):LMWH (90,000IU) granules were formulated at 355.6 mg/g SNAD, 593.4 mg/g LMWH, 50.0 mg/g Explotab, and 1.0 mg/g SLS for a total weight per unit of 1000mg. SNAD, LMWH and Explotab were bag blended for 3 minutes and transferred to a Kenwood mixer. The SLS was dissolved in 5mls of deionised water and

15   this was added to the Kenwood using a syringe. Deionised H_2O was subsequently added until the granulation end-point was reached (total 46mls). The granulate was transferred to an oven and tray dried for 18 hours at 70°C. The granulate was weighed after drying and passed through a 630µm screen on an oscillating granulator. Granule flow properties were assessed to determine the suitability of the granules for tabletting.

20   The granules were analysed for SNAD and LMWH potency content.

The tablet blend for SNAD (1100mg):LMWH (90,000IU) consisted of (w/w%) 87% granules, 7% SNAD, 5% Explotab, 0.5% Aerosil, and 0.5% Mg Stearate. The Aerosil was blended with some of the SNAD and sieved through a 1000µm sieve into the remaining SNAD. Extra SNAD (7%) was included in the formulation extragranularly

25   to make up for the apparent SNAD shortage in the granules indicated by SNAD potency analysis. SNAD : LMWH granules and Explotab were added to the mix and all components were bag blended for 3 minutes. Magnesium stearate was then added followed by bag blending for another minute. Tabletting was carried out on a 16 station piccola tablet press with two punches operating fitted with 13mm round concave

30   punches. The resulting tablets were round khaki green tablets with dark green and white flecks which were well compressed and shiny in appearance. The potency of both

-45-

SNAD and LMWH in the tablets were determined. In addition, tablet weight uniformity, hardness and disintegration time were determined.

The tablet blend for SNAD (550mg):LMWH (90,000IU) consisted of (w/w%) 94% granules, 5% SNAD, 5% Explotab, 0.5% Aerosil, and 0.5% Mg Stearate and the tablets
5   were formed similarly to the SNAD(1100mg) strength given above.

Thus, the granules were formulated into tablet blends which displayed good flow properties and greater apparent densities than the SNAD starting material (0.26gcm³). The tablet blends were compressed to form good quality tablets which showed no tendency towards capping or chipping. The SNAD (1100mg) tablets fell within 96.5 –
10   104.1% of the target tablet weight range, while the SNAD (550mg) tablets fell within 98.9 – 100.9% of the target tablet weight range. The SNAD potency of both batches of tablets were >94% of the theoretical potency. Disintegration times for both tablet batches were both < 13 minutes in deionised water.

As described in Example 7, the SNAD (1100mg) tablets were administered in a
15   three tablet dose to beagle dogs to provide a total dose of 1100mg of SNAD and 90, 000IU of LMWH. The SNAD (550mg) tablets were administered in a two tablet dose to beagle dogs to provide a total dose of 550mg of SNAD and 90, 000IU of LMWH.

Example 7:   Administration of SNAD/Heparin USP and LMWH solid oral dosage forms to dogs

20   Dogs (n=12) were divided into two group (n=6) and each group was dosed with three different formulations (cross over with a 1 week interval) as follows:

Group 1:

Day 0   Uncoated USP heparin tablet (90,000 IU + 550 mg SNAD); two tablets/dog

Day 7   LMW Heparin solution (90,000 IU + 550 mg SNAD in water); 10 ml/dog

Day 14   Uncoated LMW heparin tablet (90,000 IU + 550 mg SNAD); two tablets/dog
Group 2:

Day 0   LMW heparin subcutaneous (5000 IU in 0.5 ml saline)

Day 7   LMW Heparin solution (90,000 IU + 1100 mg SNAD in water); 10 ml/dog

Day 14   Uncoated LMW heparin tablets (90,000 IU + 1100 mg SNAD); 3 tablets/dog

-46-

Figure 5 shows the mean antifactor Xa levels versus time for the six treatments given above. High antifactor Xa responses were observed in all groups dosed with LMW heparin relative to USP heparin. The antifactor Xa levels following LMW heparin subcutaneous injection (5000 IU) were higher than those following USP heparin

5   injection (approximately 6500 IU). Similarly, antifactor Xa levels for LMW heparin tablets (90,000 IU + 550 mg SNAD) were higher than those of USP heparin. The % bioavailability (calculated using AUC_{0-8} IU/ml/h) of the studied groups shows that 1) uncoated tablets exhibited similar (for 550 mg SNAD) or higher (for 1100 mg SNAD) bioavailability relative to their solution legs and 2) an increase in systemic availability

10   was observed with increase in SNAD dose (from 3.24% for 550 mg SNAD to 6.55% for 1100 mg SNAD).

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing

15   description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

-47-

CLAIMS

What is claimed is:

1. A solid oral dosage form comprising
    i) a heparin drug in admixture with
    ii) a carrier, wherein the carrier is selected from the group consisting of SNAC, SNAD, pharmaceutically acceptable salts thereof, esters thereof and combinations thereof,

    wherein the dosage form protects the carrier during transit through the low pH regions of the GI track.

2. A solid oral dosage form comprising
    i) a heparin drug in admixture with
    ii) a carrier, wherein the carrier is selected from the group consisting of SNAC, SNAD, pharmaceutically acceptable salts thereof, esters thereof and combinations thereof, and
    iii) at least one rate controlling polymer material,

    wherein the dosage form protects the carrier so as to facilitate enhanced absortion of the heparin drug.

3. The solid oral dosage form according to either Claim 1 or Claim 2, wherein the dosage form is a tablet or a multiparticulate dosage form.

4. The solid oral dosage form according to any of the previous claims, wherein the heparin drug and the carrier are present in a ratio of from 1:100 to 100:1 (drug : carrier).

5. The solid oral dosage form according to Claim 3, wherein the multiparticulate dosage form comprises a plurality of discrete particles, pellets, mini-tablets or mixtures or combinations thereof.

-48-

6.   The solid oral dosage form according to Claim 3, wherein the tablet or multiparticulate dosage form is coated with one or more coatings.

7.   The solid oral dosage form according to Claim 6, wherein the one or more coatings comprise a rate controlling polymer material.

8.   The solid oral dosage form according to Claim 5, wherein the dosage form comprises a blend of two or more populations of particles, pellets, mini-tablets or mistures or combinations thereof having different *in vivo* or *in vitro* release characteristics.

9.   A solid oral dosage form according to either of Claims 5 or 8, wherein the particles, pellets or mini-tablets are filled into hard or soft gelatin capsules.

10.   A method of treatment for a medical condition in need of a heparin drug compriing administering to a patient suffering from said condition a therapeutically effective amount of the solid oral dosage form according to any of Claims 1 to 9.

11.   Use of a heparin drug and a carrier in the manufacture of a medicament for the treatment of a medical condition treatable by the heparin drug, wherein the heparin drug and the carrier are in the form of a solid oral dosage form according to any of Claims 1 to 9.
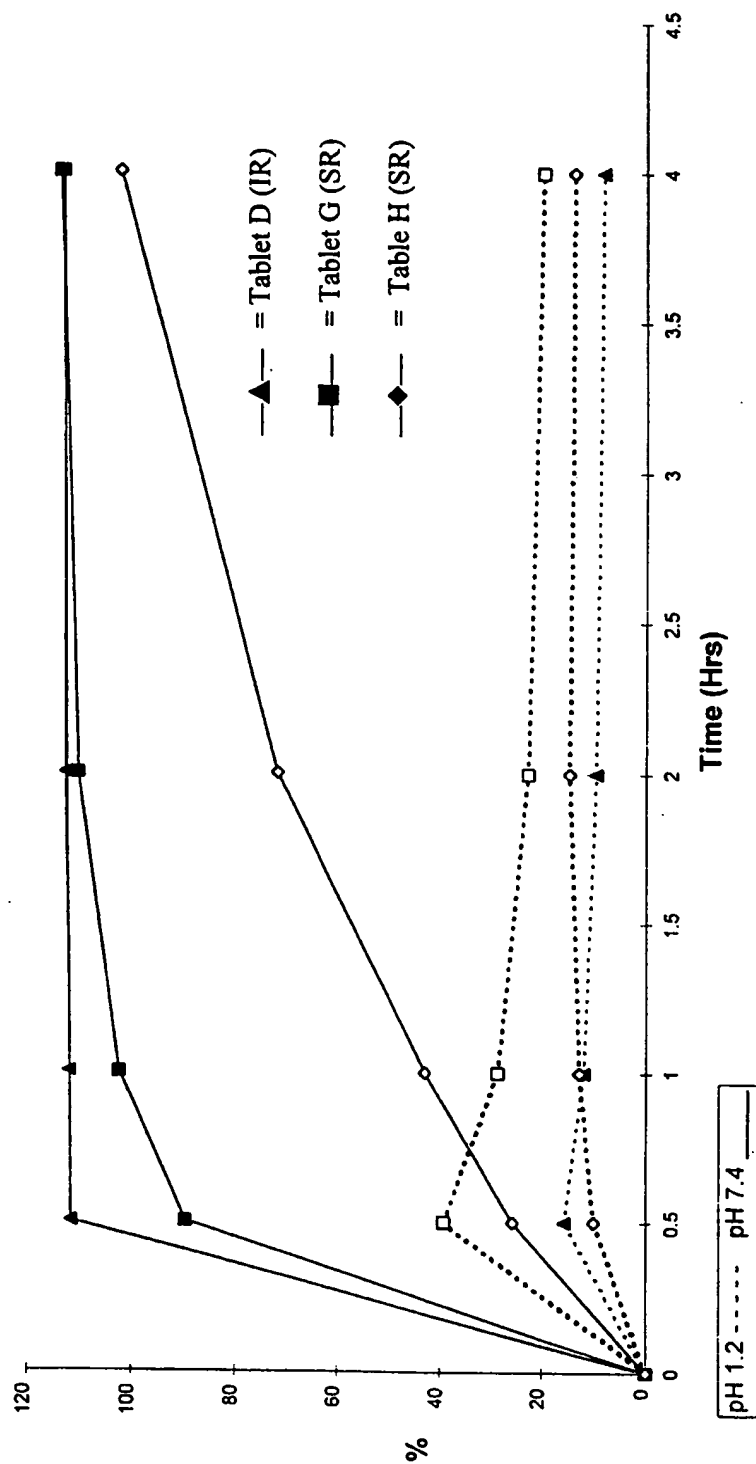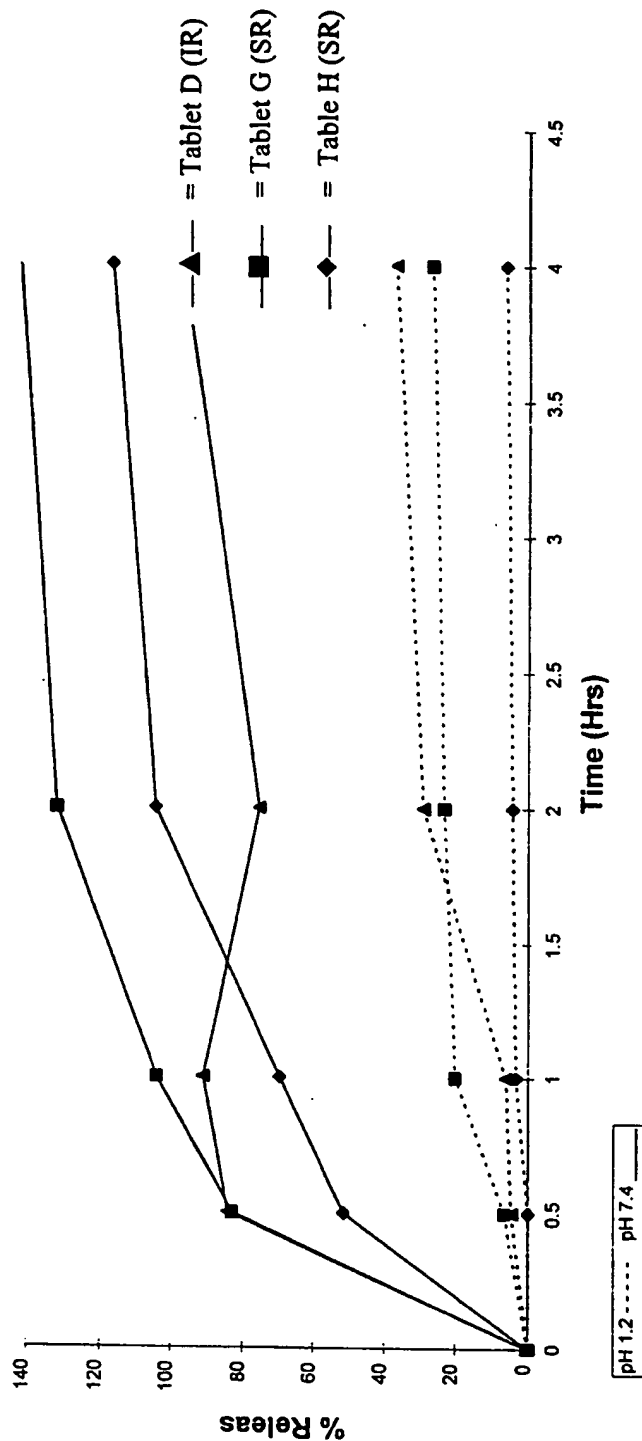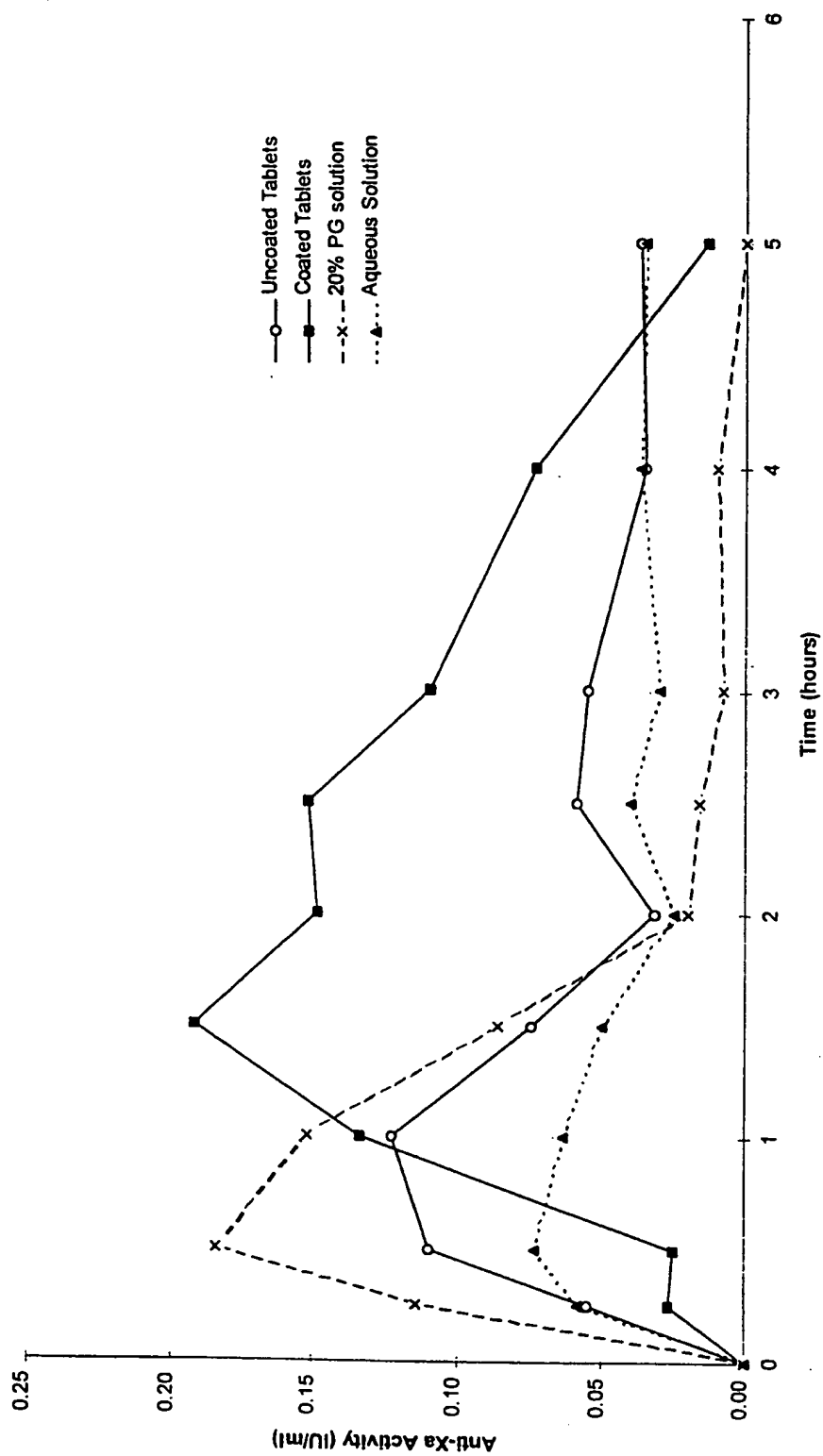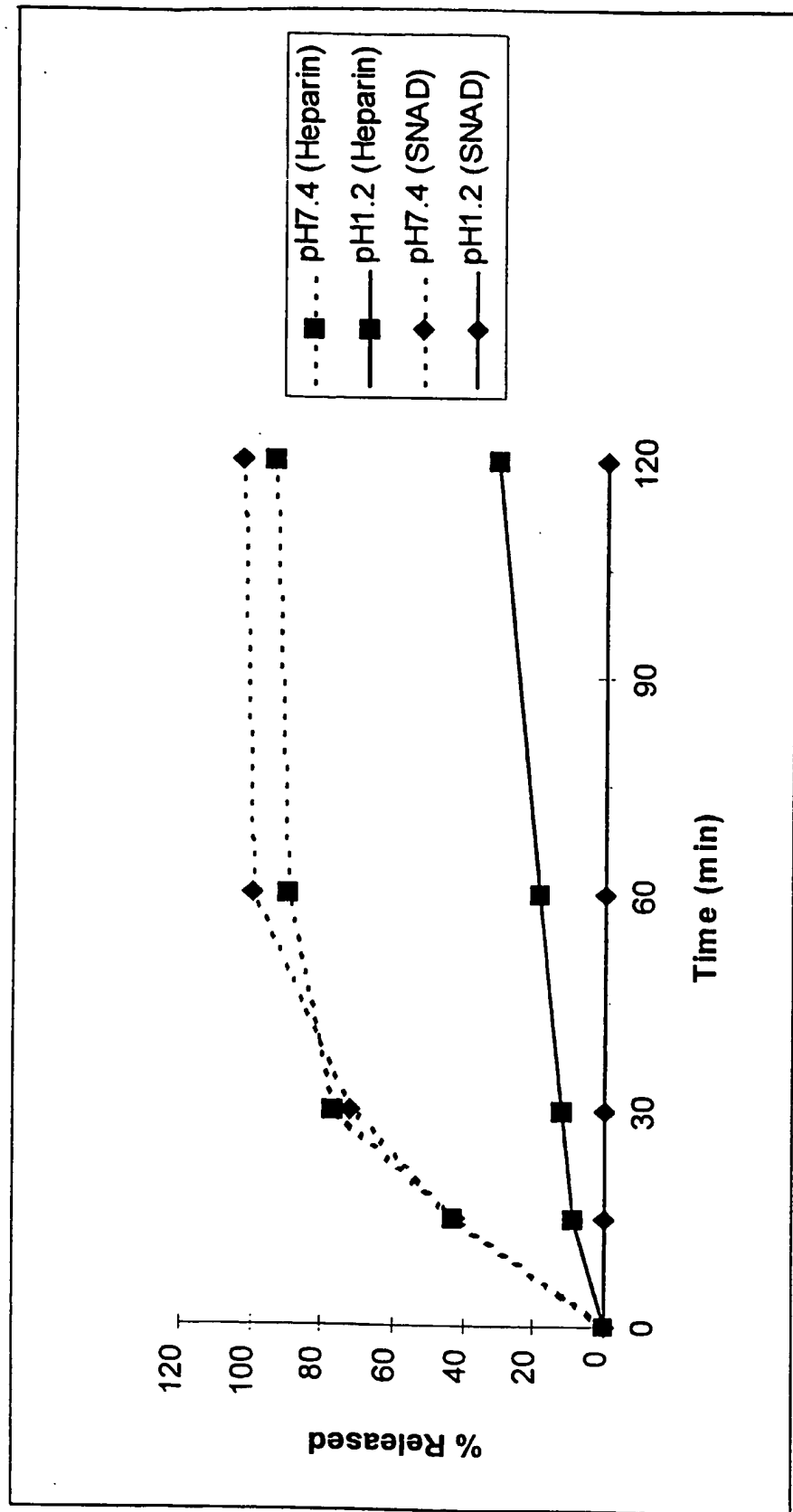
Figure 1

Figure 2

Figure 3

Figure 4
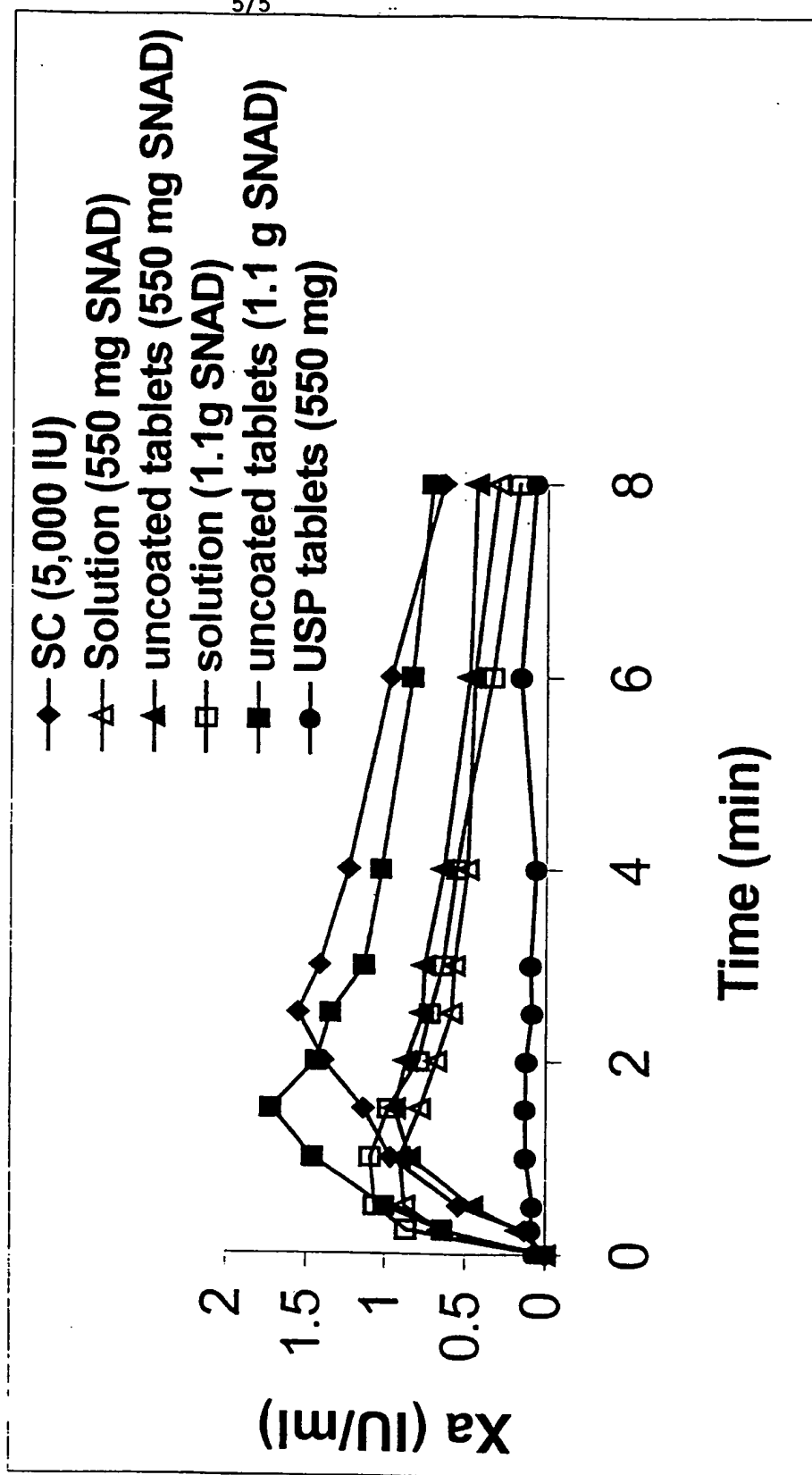
Figure 5

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/19, 31/195
US CL :514/557, 559, 561, 567, 568
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/557, 559, 561, 567, 568

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST
heparin, heparinoid, SNAC, SNAD, 8-(salicyloylamino)octanoic acid, 10-(salicyloylamino)decanoic acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 6,001,347 A (LEONE-BAY et al.) 14 December 1999, see entire document.	1-11
Y	US 5,650,386 A (LEONE-BAY et al.) 22 July 1997, see entire document.	1-11

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

* Special categories of cited documents:	'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'A' document defining the general state of the art which is not considered to be of particular relevance	
'E' earlier document published on or after the international filing date	'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
	'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
'O' document referring to an oral disclosure, use, exhibition or other means	
'P' document published prior to the international filing date but later than the priority date claimed	'A' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 MAY 2000	06 JUN 2000

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